

KETEK CLINICAL STUDY FRAUD: WHAT DID AVENTIS KNOW?

HEARING BEFORE THE SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS OF THE COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES ONE HUNDRED TENTH CONGRESS

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KETEK CLINICAL STUDY FRAUD: WHAT DID AVENTIS KNOW?

TUESDAY, FEBRUARY 12, 2008

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 11:06 a.m., in room 2123, Rayburn House Office Building, Hon. Bart Stupak [chairman of the subcommittee] presiding.

Present: Representatives Stupak, Dingell, Ex Officio, Walden, Burgess, and Barton, Ex Officio.

Also Present: Representatives Markey and Shimkus.

Staff Present: John Sopko, Joanne Royce, David W. Nelson, Kyle Chapman, Scott P. Schloegel, Alan Slobodin, and Karen E. Christian.

OPENING STATEMENT OF HON. BART STUPAK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. STUPAK. This meeting will come to order. Today, we have a hearing titled Ketek Clinical Study Fraud: What Did Aventis Know?

Before I begin, I have a couple of housekeeping items to discuss. On January 29, the subcommittee held a business meeting to issue subpoenas for several outstanding requests the Committee has made of the FDA. The subpoenas were approved unanimously on a 12-0 bipartisan vote.

While we are pleased that the FDA has produced the agents for today's hearing, we are far less than pleased with the response received yesterday to the committee regarding our subpoena for documents requested almost a year ago, in March of 2007.

Yesterday afternoon, a letter arrived to the committee signed by an assistant secretary for legislation at the Department of Health and Human Services, and signed by the chief of staff for the FDA, stating that they want to, quote, "reach alternative solutions," end of quote, rather than producing the documents we subpoenaed at our January 29 business meeting.

The letter is troubling on several fronts. First, the subpoena was served to the Secretary of Health and Human Services, and he did not provide the Committee the courtesy of a response under his signature. Second, there appears to be a continued effort to keep secret the documents we requested. This only causes members to further question what could be so damaging in the materials that the Administration wants to stonewall our bipartisan subpoena.

There is precedent for obtaining briefing book documents from both Democratic and Republican administrations without having to issue a subpoena. The Secretary was made aware of the precedents. With the committee chaired by Republicans Mr. Bliley and Mr. Barton, we received briefing books of FDA commissioners in a Democratic administration, Dr. Kessler. They were also obtained when chaired by a Democrat, Mr. Dingell, receiving briefing books of a commissioner in a Republican administration, Mr. Frank Young.

I find the letter received yesterday to be very disconcerting, and will be discussing options with Chairman Dingell and Ranking Members Barton and Shimkus in the coming days.

On a separate note, due to a series of votes in the Senate, we will need to call our second panel first and have Senator Grassley present his testimony as our second panel. Or when the Senator gets here, we will move to his testimony.

Right now, let's begin this hearing. Each member will be recognized for 5 minutes for an opening statement.

I will begin.

Today, we hold the third hearing by the subcommittee on whether the FDA can fulfill its mandate to protect American people from unsafe drugs. Once again, we will be exploring this question in the context of the controversial antibiotic, Ketek.

The deeper the members of this subcommittee dig into the Ketek approval process, the more disturbed we become about the entire drug approval process. Today's hearing will shine a spotlight on a little-understood and rapidly growing world of private drug research and clinical trials. Specifically, we will examine the data integrity lapses and fraud contained in the large Ketek clinical trial, Study 3014, which was initially commissioned to assure the safety of Ketek.

The Ketek clinical study illustrates the failure by all stakeholders—FDA, drug companies, third-party monitors, and institutional review boards—to ensure the integrity of clinical trials used to support the safety and approval of new drug applications.

A year ago, this committee heard testimony from Senator Charles Grassley about his repeated attempts to secure information from the FDA and the obstacles the FDA erected to impede his investigation of the Ketek approval process. Senator Grassley also expressed concern that FDA management discourages, even muzzles, scientific dissent. Sadly, this committee's parallel investigation of Ketek over the past year has confirmed Senator Grassley's dismal assessment of the FDA.

Senator Grassley returns today to share the findings contained in his recently issued report of the Finance Committee's ongoing investigation into the safety of Ketek, particularly what he has uncovered regarding the criminal investigations conducted by FDA's Office of Criminal Investigations, OCI, into allegations of fraud in connection with Ketek Clinical Study 3014.

We also welcome back Ann Marie Cisneros, formerly a senior clinical research associate with PPD, the contract research organization, CRO, hired by Aventis to monitor Study 3014. Ms. Cisneros will open the second panel by explaining why she was convinced that Aventis, PPD and Copernicus, the institutional review board,

all charged with protecting the patients in Study 3014, were well aware of the faulty and possibly fraudulent data submitted to the FDA by Aventis in connection with the approval of Ketek. We are particularly grateful to Ms. Cisneros for sharing her experience with this committee, despite attempts by her former employer to extort her silence.

Ms. Cisneros was dispatched in February 2002 to inspect the site of Dr. Kirkman-Campbell, who enrolled more patients—407, to be exact—into Study 3014, more than any other investigator. Prior to her visit, Ms. Cisneros was informed by Dr. Reynolds of extremely suspicious activity at the site by other PPD personnel and was asked to scrutinize Dr. Kirkman-Campbell's site and try to bring back evidence of fraud.

After only 2 days at the site, Ms. Cisneros found the site so troubling that she was afraid that Dr. Kirkman-Campbell was endangering patient safety. Consequently, on February 21, 2002, Ms. Cisneros called Copernicus, the institutional review board working for Aventis, to urge them to intervene to protect patients. Copernicus did nothing.

Dr. Kirkman-Campbell was ultimately convicted of fraud in connection with Study 3014 and sentenced to nearly 5 years in prison.

The fraud at the site was detected only after a routine audit by the FDA, not because Copernicus or Aventis had warned them. Well before the FDA audit, however, Aventis, PPD, and Copernicus were all aware of scientific misconduct indicative of fraud at the site.

Evidence before this committee suggests that only a company intent upon ignoring the obvious could have failed to detect fraud in Study 3014. At Kirkman-Campbell's site alone obvious indicators of fraud included the following: errors in nearly every informed consent form—date modifications, initials different from the signatures, study coordinator entering dates for subjects and the principal investigator; blatantly forged signature on informed consent forms; very limited medical records; use of different color ink on medical charts—overwrites, cross-outs—inserts of diagnoses in different colored ink; routine failure to give pregnancy tests to women of child-bearing age; study investigator and coordinator unaware of definitions of serious adverse event or adverse event special interest; no adverse events for the first 300 patients enrolled with drugs known to have adverse events; lab results indicative of blood splitting; lack of proper diagnosis for study eligibility; husbands and wives enrolling together; large number of patients randomized in the Interactive Voice Response System in a short increment of time when the office was closed for lunch and not seeing patients; and 100 percent compliance by patients taking study medication.

Aventis, PPD, and Copernicus were aware of this misconduct well before Aventis submitted Dr. Kirkman-Campbell's data to the FDA to support the approval of Ketek. At a minimum, Aventis should have discontinued enrollment at the site and notified the FDA.

We will also hear today from three FDA criminal investigators who investigated misconduct and/or fraud in connection with Ketek Study 3014.

The FDA has done its very best to deny this committee access to these agents and their investigatory documents. These agents testify today under subpoena. Be assured, however, that we do not lightly compel the appearance of witnesses before this subcommittee to discuss criminal investigative matters and would not have done so were their testimony not of the utmost importance.

I would like to remind FDA managers that retaliation against any agent for their testimony will not be tolerated by this committee.

Office of Criminal Investigation Special Agent Robert West led the criminal investigation which resulted in the August 2003 indictment and October 2003 conviction of Dr. Kirkman-Campbell for fraud in connection with Study 3014. Special Agent West will explain how he tried to convince FDA management in 2003 to expand the investigation of fraudulent submission of trial data to include other sites and, ultimately, Aventis. However, FDA did not open an investigation into possible misconduct of Aventis until 2006, over 4 years after the study ended.

In early March 2006, Special Agent Robert Ekey was assigned the criminal investigation of Aventis. Today, he will confirm that his investigation revealed evidence indicating that Aventis was aware of serious data integrity problems at the Kirkman-Campbell site, but submitted the site data to the FDA, notwithstanding.

The investigation languished until shortly after this committee's Ketek hearing last year, when the case was reassigned to Special Agent Douglas Loveland. Special Agent Loveland conducted an extensive reinvestigation, and became convinced of Aventis' guilt. On June 21, 2007, he presented FDA's evidence of Aventis to the United States attorney for the District of New Jersey and recommended prosecution. The U.S. Attorney ultimately declined to prosecute Aventis, not because of lack of evidence against Aventis; the declination letter states instead, Put simply, FDA's lack of reliance on the faulty study and its subsequent decision to approve Ketek despite ongoing investigation into Dr. Kirkman-Campbell's conduct make any conviction against Aventis for fraud in connection with the submission of the study highly unlikely.

Our final panel consists of the following industry officers: Dr. Paul Chew, President of U.S. Research and Development, Sanofi-Aventis Pharmaceuticals; Fred Eshelman, CEO of PPD, the contract research organization hired by Aventis to monitor Study 3014; and Sharon Hill Price, the CEO of Copernicus Group, an institutional review board hired to protect human subjects of Study 3014.

Evidence before this committee suggests that each of these firms had direct knowledge of serious misconduct and possible fraud in Study 3014, yet none of them notified the FDA. We expect them to explain why they did not do so.

Clinical research has changed dramatically within the last 2 decades. No longer anchored in public sector, clinical trial practice like PPD and Copernicus Group is currently big business and largely self-regulating. Today's hearing will demonstrate how some actors behave in a climate of self-regulation.

It may be time to seriously rethink the regulatory framework for the clinical trial industry and institutional review boards and contract research organizations.

That concludes my opening statement.

Mr. STUPAK. I next would like to turn to my colleague, Mr. Walden, for his opening statement, and thank you for being here today.

OPENING STATEMENT OF HON. GREG WALDEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Mr. WALDEN. Thank you very much, Mr. Chairman, for calling this hearing so our committee can continue to shine a light on what transpired with Aventis' large safety trial of its antibiotic Ketek.

Protecting the integrity of the FDA drug approval process is a priority for me and for all members of this committee. In order to achieve this, each and every person involved in the drug approval process must strictly adhere to the highest standards of conduct and maintain an unquestionable level of ethics.

Unfortunately, from what this committee has learned through its year-long investigation of the issues and problems raised by the review and approval of Ketek, it appears that standards of conduct and ethics were only optional. Well before the time I arrived here in Congress, Chairman Dingell shepherded legislation through this House that granted the FDA the power to debar or, essentially, blacklist companies and individuals who are convicted of felonies for misconduct relating to the regulation of drug products. Individuals who are debarred, or disqualified by the FDA are then listed on the FDA Web site.

Now, it is my understanding that some of the companies testifying here today rely on those lists when selecting physicians to serve as investigators in clinical trials, as they rightly should. Debarment is a powerful tool that FDA can use to protect the integrity of the drug approval process, and I applaud Chairman Dingell for giving FDA that authority. However, a minority committee staff report released yesterday shows that the FDA has failed to initiate debarment proceedings against several individuals and companies even when the basis for debarment, such as conviction of fraud for clinical trial misconduct, clearly exists. By failing to do so, individuals that are currently incarcerated, that are currently sitting in jail for felonies they committed, are still eligible to participate in administration of clinical trials. This is outrageous.

When the FDA does pursue debarment, it is in a delayed or perhaps even a lackadaisical manner. According to the staff report, an average of 38 months passes between the date of conviction and the date that the FDA begins debarment.

The FDA has a mandate to protect the American people from unsafe drugs and, as such, it must make it a priority to use its authority to immediately ban companies and individuals who are convicted of crimes that could jeopardize the safety of drugs from continuing to do business before the FDA. Both the FDA and the drugmakers that are developing new drugs must remain vigilant in their efforts to detect and eliminate fraud.

Hopefully, today's hearing will help us understand what went wrong with Ketek Study 3014 and how we can make sure those mistakes and errors never happen again.

Chairman Stupak, thank you for convening this hearing and your diligent work on this issue. And I yield back the balance of my time and look forward to hearing from all of our witnesses.

Mr. STUPAK. I thank the ranking member.

Mr. STUPAK. I would next call on the chairman of the full committee, Mr. Dingell, for an opening statement, please.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. DINGELL. Mr. Chairman, thank you for continuing to pursue this matter and for your leadership. I commend you for the vigor with which you are approaching these matters.

I would like to remind all and sundry that this is an oversight hearing which will be conducted within the traditions and practices of this committee. It will be our expectation that all persons called upon to participate, either by deliverance of testimony or by presentation of books, papers and records, will cooperate.

I would remind all and sundry that this is a proceeding which is being conducted in a bipartisan fashion; and we will address that matter a little further. This committee has, and this subcommittee has, a tradition of proceeding to see to it that the business of the committee is properly conducted, that all persons cooperate, and that they do so in response to a fair and a bipartisan inquiry by the committee, aimed at gathering the facts to see whether the law is properly enforced and whether or not the Federal officers and employees are carrying out their responsibilities in proper fashion.

We also are looking into seeing whether or not the committee is receiving proper information, but also as to whether or not the committee will find it necessary to enforce its subpoenas in an appropriate way, looking to the possibility of not only seeing to it that the law is properly being enforced and carried out, but as to whether or not additional legislative work by the committee is required in order to see to it that the public is properly protected.

We have here a question relating to the ill-advised approval of the antibiotic Ketek. Beyond the harm to the public health from millions of prescriptions written on this drug by doctors who relied on the FDA, this investigation raises questions about the integrity of the drug approval process and those who have engaged in that process.

FDA is supposed to receive clinical data from manufacturers who have properly conducted designed studies that prevent serious misconduct or fraud. If FDA knows or suspects such fraud exists and then ignores it, then this committee has the duty to probe as deeply as necessary to determine whether the entire approval process itself has been compromised.

Further, this committee expects the full cooperation from Federal agencies when we carry out our oversight responsibility to ensure that such agencies enforce the laws enacted by the Congress in a proper way.

Given the allegations of wrongdoing in the Ketek matter, we have the duty to compel FDA and the Department of Health and Human Services to cooperate fully in the inquiries of the com-

mittee. Instead, this committee and other committees in the Congress have been repeatedly stonewalled on this matter.

Our good friend, Senator Grassley, who will be appearing here before the committee, the former chairman of the Senate Committee on Finance, who is testifying before us today, initiated inquiries into Ketek during the last Congress. He encountered the same bad faith and obstruction from the administration.

Three of the witnesses today are FDA criminal investigators who uncovered the fraud and misconduct that is the subject of our hearing. Unfortunately, the committee had to subpoena them to testify at this hearing because Food and Drug Commissioner von Eschenbach and Secretary Leavitt refused to allow them to appear here voluntarily. A similar refusal thwarted Senator Grassley's effort in the last Congress.

This committee will not tolerate actions by the administration which would thwart a proper inquiry by this body. It is to be observed that, fortunately, with a bipartisan vote of 12-0 by this subcommittee, we issued subpoenas to these witnesses.

My good friend, Mr. Joe Barton, the ranking member, and I have given the agency every opportunity to avoid this embarrassment, but apparently to no avail. Unfortunately, this obstructionist behavior continues. Just yesterday we received a letter from the Secretary's office, which I ask at this time, Mr. Chairman, be made a part of the hearing record.

Mr. STUPAK. Without objection, Mr. Dingell.

[The information appears at the conclusion of the hearing.]

Mr. DINGELL. In that letter, the members of the Secretary's staff announced his refusal to honor the subpoena of the subcommittee for records relating to Food and Drug Commissioner von Eschenbach's briefing books.

I want to remind my colleagues that similar records have been turned over to me, as well as to my good friend Mr. Barton, by both Republican and Democratic administrations in bipartisan investigations at FDA and other agencies in the executive branch. I must also remind all that these records were unanimously subpoenaed by this subcommittee with a bipartisan vote of 12 to nothing.

I ask my colleagues to then scrutinize Secretary Leavitt's arguments in refusing to honor the subpoenas of the subcommittee. At best, I note they are specious. At worst, they are contemptuous of the Congress and of the committee. If anything, the refusal of the Secretary to cooperate causes me to wonder, what is the Secretary trying to hide? What is in these briefing books that he does not want either my Republican colleagues or my Democratic colleagues to see? Is there evidence of perjury? Are the statements embarrassing to the Administration?

In any event, it is the right of this committee to have them, and we will do so. Let me make it clear on this point. Neither Chairman Stupak nor I, nor our colleagues of this committee on either side will tolerate a perversion of congressional powers to investigate and to probe. I fully support Chairman Stupak's request to enforce this subpoena by holding Secretary Leavitt in contempt.

Mr. Chairman, there is an easy way for the agency to undergo congressional oversight. There is also a hard way. Commissioner von Eschenbach and Secretary Leavitt appear to have chosen the

latter. I caution both gentlemen to reconsider their ill-conceived notion of congressional oversight and to allow the bipartisan policies that have long been the practice of this committee to be used for the service of the public interest.

I yield back the balance of my time and I thank you, Mr. Chairman.

Mr. STUPAK. I thank the gentleman.

[The prepared statement of Mr. Dingell follows:]

STATEMENT OF HON. JOHN D. DINGELL

Mr. Chairman, thank you for continuing to pursue the truth regarding the Food and Drug Administration's (FDA) ill-advised approval of the antibiotic Ketek. Beyond the harm to the public health from millions of prescriptions written for this drug by doctors who relied on the FDA, this investigation raises questions about the very integrity of the drug approval process.

FDA is supposed to receive clinical trial data from manufacturers who have conducted properly designed studies that prevent serious scientific misconduct or fraud. If FDA knows or suspects such fraud and then ignores it, this Committee has every reason to probe as deeply as necessary to determine whether the entire approval process itself has been compromised.

Further, this Committee expects the full cooperation from Federal agencies when we carry out our oversight responsibility to ensure such agencies enforce the laws enacted by Congress. Given the allegations of wrongdoing in the Ketek matter, we have every right to expect FDA and the Department of Health and Human Services (HHS) to cooperate.

Instead, this Committee and other committees in Congress have repeatedly been stonewalled. Our good friend Senator Grassley, the former Chairman of the Senate Committee on Finance, who is testifying before us today, initiated inquiries into Ketek during the last Congress. He encountered the same bad faith and obstruction from this Administration.

Three of the witnesses today are FDA criminal investigators who uncovered the fraud and misconduct that will be the subject of our hearing. Unfortunately, they had to be subpoenaed to testify at this hearing because Food and Drug Commissioner von Eschenbach and Secretary Leavitt refused to allow them to appear here voluntarily. A similar refusal thwarted Senator Grassley's inquiry in the last Congress. Fortunately, with a bipartisan vote of 12-0 by this Subcommittee, we issued subpoenas for these witnesses. My friend Joe Barton, the ranking Member, and I gave the agency every opportunity to avoid this embarrassment, but to no avail.

Unfortunately, this obstructionist behavior continues. Just yesterday we received a letter from Secretary Leavitt's office, which I ask to be made part of the hearing record.

In that letter, his minions announced his refusal to honor our subpoena for records relating to Food and Drug Commissioner von Eschenbach's briefing books. I must remind my colleagues that similar records have been turned over to me, as well as my good friend Joe Barton, by both Republican and Democratic Administrations. I must also remind you that these records were also unanimously subpoenaed with a bipartisan vote of 12 to 0.

I ask my colleagues to analyze Secretary Leavitt's arguments in refusing to honor your subpoena. At best, they are specious. At worse, they border on contempt of Congress. If anything, his refusal to cooperate causes me to wonder what he is trying to hide? What is in those briefing books that he does not want either my Republican colleagues or our side to see? Is there evidence of perjury? Are there statements embarrassing to the Administration?

Let me be clear on this point. Neither Chairman Stupak nor I will tolerate such a perversion of congressional powers to investigate and probe. I will fully support Chairman Stupak's request to enforce this subpoena by holding Secretary Leavitt in contempt.

Mr. Chairman, there is an easy way for any agency to undergo congressional oversight. There is also a hard way. Commissioner von Eschenbach and Secretary Leavitt appear to have chosen the latter. I caution both gentlemen to reconsider their ill-conceived notion of Congressional oversight and follow the bipartisan policies that have long been the practice of this Committee.

Mr. STUPAK. Mr. Shimkus is delayed because of weather, but hopefully he will be here later today.

Mr. WALDEN. Mr. Chairman, do you want to make a motion?

Mr. WALDEN. Mr. Chairman, I have his opening statement that I would like to have inserted into the record.

Mr. STUPAK. Mr. Shimkus's opening statement will be made a part of the record, as will the opening statement of all members of the subcommittee. Your statement will be made part of the record when they arrive or if they are presented to the committee.

[The prepared statement of Mr. Shimkus follows:]

STATEMENT OF HON. JOHN SHIMKUS

Thank you Chairman Stupak for convening this hearing to further examine the issues surrounding the antibiotic Ketek ("KEE-tek"), and how to protect the integrity of the FDA regulatory process.

Today's hearing focuses on the conduct of Aventis Pharmaceutical Company, a drug company that was the subject of a criminal investigation. In the end, this investigation did not result in a prosecution.

I think we are all trying to achieve the same thing in this investigation: we want a FDA drug review and approval process that promotes and protects the integrity of data gathered during clinical trials. But we will never achieve this goal if the individuals and companies who are prosecuted and convicted of crimes for misconduct in criminal trials are never debarred by FDA.

Fifteen years ago, our colleague, Chairman Dingell, spurred the passage of the Generic Drug Enforcement Act. Through that Act, Congress gave FDA the power to debar companies and individuals who are convicted of felonies for misconduct relating to the regulation of drug products. Individuals who are debarred or disqualified by FDA are then listed on the FDA website. It is my understanding that some of the companies testifying here today rely on those lists when selecting physicians as investigators in clinical trials.

However, as a report prepared by Minority Committee Staff and released yesterday shows, FDA has failed to initiate debarment proceedings against several individuals and some companies even when the basis for debarment clearly exists. It has also initiated debarments in an uneven way; the Staff Report cites more than one example where FDA pursued debarment in one case, but did nothing in another case where the underlying facts and convictions were similar. FDA also takes years to initiate debarment proceedings after conviction; according to the staff report, an average of 38 months passes between the date of conviction, and the date FDA begins debarment. The delay has very real consequences for public health, as an investigator convicted of a felony relating to clinical trial misconduct can continue to receive investigational drug products and participate in trials up to the date debarment is finally imposed.

As we now know, Dr. Kirkman-Campbell, one of the investigators in the Ketek trial, was indicted on fraud charges for her misconduct in Study 3014. During our investigation of Ketek, Minority Committee staff learned that, despite the fact that Kirkman-Campbell had been convicted of a felony and incarcerated in federal prison, FDA had never debarred her. In fact, she is still not debarred today, even though FDA initiated debarment proceedings against her almost one year ago. This means that under federal law, she is still eligible to participate in clinical trials, even though she is currently incarcerated.

We should not be surprised when there is a lack of vigilance and awareness of fraud when the industry's regulator does not make it a priority to ban companies and individuals who are convicted of crimes from continuing to do business before FDA. We need to have a system in which pharmaceutical companies and clinical trial patients can have confidence. For this reason, Ranking Member Barton will pursue legislation that strengthens FDA's debarment authority. Under this legislation, FDA will have authority over not only generic drug companies, but any company doing business before FDA. The Act will also clarify that FDA will have authority to debar companies not just for their misconduct relating to the development and approval of a drug application, but any misconduct relating to the regulation of the drug. We should hold companies and individuals who do business before FDA to the same standard, without respect to the type of drug product. I look forward to providing Ranking Member Barton with whatever assistance I can to help with this important bill. I hope my colleagues on this Committee will do the same.

I am looking forward to the testimony from the companies involved in the Ketek safety trial: Dr. Paul Chew for Aventis, the sponsor; Dr. Fred Eshelman, of PPD, the study monitor; and Sharon Hill Price from Copernicus, the institutional review board. I expect that each of these witnesses will provide a candid assessment of their work during the trial; the procedures they had in place to detect and identify fraud; and how they dealt with concerns about fraud. Hindsight is always twenty-twenty. But even cursory review of the monitoring reports and emails exchanged among the parties during Study 3014 shows that the parties were aware that fraud was a possibility as early as January 2002—a full seven months before Aventis submitted the results of the study to FDA.

We want to know why Aventis felt it was appropriate to include data from Dr. Kirkman-Campbell's site, as well as other sites where the suspicion of fraud was raised, in its July 2002 report on Study 3014 without noting the number of Good Clinical Practice violations and protocol violations. I understand that Study 3014 was a safety study, and that the point of the study was to collect as much data as possible on adverse events related to Ketek. However, in a case such as this where Clinical Practice Violations, fraud allegations, and other violations exist to a degree that may affect data integrity, at what point should a company begin to question the safety data? I would also like a better understanding of the roles of the study monitor, PPD, and the institutional review board, or IRB, Copernicus, in selecting the physicians who participate in the study and dealing with the problems and violations that presented during the study.

We are also joined today by the FDA criminal investigators who were assigned to investigate the allegations of fraud in Study 3014: Robert West, Robert Ekey, and Douglas Loveland. Two weeks ago, the Republicans on this Subcommittee supported Chairman Stupak's motion to subpoena the testimony of these criminal investigators. As the investigators who have interviewed the major players in the Ketek safety trials, your testimony is critical to helping us have the best possible understanding of the evidence in this case.

Finally, I would like to thank Senator Chuck Grassley, for taking the time to be with us this morning. Senator Grassley has been investigating the Ketek safety trials and FDA's review and approval of Ketek for the last three years. I look forward to his testimony.

Hopefully, today's hearing will help us understand what went wrong in Study 3014; whether those mistakes and errors could have been prevented; and how we can make sure they never happen again.

I thank Chairman Stupak for convening this hearing and yield back the balance of my time.

Mr. STUPAK. Mr. Burgess for an opening statement, please.

**OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Dr. BURGESS. Thank you, Mr. Chairman. Mr. Chairman, I want to apologize in advance because I do have to leave this hearing early. Congress doesn't vote until much later this afternoon, but when this hearing was scheduled, I had made previous plans to travel to another key Federal agency over which this committee also has oversight.

But I do believe this is an important hearing, and I only wish it had been scheduled when there was availability for more members to attend.

Today, we are here to continue our discussion regarding the approval process for the antibiotic Ketek. When I was practicing medicine for over 20 years, my patients relied on me to administer safe medicine. In return, I relied upon the Federal drug approval process. I relied on the process to be prudent and cautious. I relied on the notion that the approved drugs were safe. However, when there is a breakdown in the process, and when there are fraudulent activities, this reliance can prove dangerous.

As a physician, it is unfathomable that anyone would gamble with my patients' lives. I believe that any allegation of wrongdoing must be seriously investigated.

It is important to note that the largest enroller of Ketek, Dr. Kirkman-Campbell, is now serving 4 years in Federal prison for her wrongdoings. I think it is important also to note and to thank the leadership of this committee, as well as the leadership of Senator Grassley, for their pursuit of truth in Ketek's approval process. It is my hope that this investigation is able to shed some light on troublesome allegations, and that we never again have to learn of another Study 3014 and, more importantly, that the confidence of America's doctors and America's patients and America's mothers and fathers are not further undermined.

There are still many questions that need to be answered, and I am hopeful that the witnesses testifying before us today, including the FDA criminal investigators, as well as the companies involved in the approval process of this drug, will be able to address many of the allegations before the committee.

While, clearly, the focus of this hearing is on Ketek, I would be remiss if I did not also briefly mention the minority staff report that was issued yesterday, detailing the problems with the FDA's debarment process. The report also makes some serious allegations, including the troubling fact that Dr. Kirkman-Campbell, now a convicted felon, is still eligible to work with the FDA because she has not been debarred. According to Ranking Member Joe Barton, who issued the report, quote, "When it comes to excluding the worst of the worst, convicted felons, the Food and Drug Administration's debarment process seems to be nonexistent," end quote.

Now, the staff-prepared minority report does disclose an ongoing pattern of inaction and, perhaps, an almost institutional non-enforcement regarding the debarment proceedings. And this subcommittee, appropriately, is holding hearings. But, Mr. Chairman, I do have to say it seems like we are holding hearing upon hearing.

We are now 13 months or more into this process—apparently, some of the problems go back at least as far as 15 or 16 years—and I do have to ask the question, When are we going to get to the point where we actually legislate on this issue and stop just endless investigation after investigation?

This is the type of product that America—America's doctors, America's patients, America's moms and dads—want to see out of this committee, indeed, what they have come to expect.

I also feel it is my obligation to mention that we are now 65 years into the availability of antibiotics for treating infectious disease. Antibiotics have changed the practice of medicine.

Not every antibiotic that is out there is without risk. For example, penicillin, one of the early antibiotics to be introduced back in the early 1940s, would have a difficult time with the approval process today. I am allergic to penicillin; there is a chance I could die if I took that medication. Yet I am grateful that that medication exists.

As someone who is allergic to penicillin, I am also grateful that there is ongoing research and development of antibiotics to treat community-acquired pneumonia for individuals who are allergic to penicillin. And Ketek would fall into that category.

Other antibiotics that had been introduced, that had serious side effects, such as chloramphenicol, are now available to treat the most serious of infections; and it would be a mistake—it would be a mistake if those antibiotics were not still available. So we do have to balance what is in the broad public interest as we continue our efforts at oversight, to make certain that the FDA does indeed provide the level of commitment that we all wish it would.

Now, this committee has jurisdiction over the FDA. We have a duty to the public to review and investigate this problem and to legislate solutions for this problem. And I thank Ranking Member Barton for having the minority staff report prepared and bringing this to our attention; and I hope we can work in a bipartisan manner to investigate and resolve this issue.

Mr. Chairman, in the interests of time, I will yield back the balance of my time.

Mr. STUPAK. Thank you, Mr. Burgess.

Mr. STUPAK. Seeing no other members, we will begin with our panel of witnesses.

On our first panel to come forward today we have Ms. Ann Marie Cisneros, former Senior Clinical Research Associate at PPD, Inc.; Mr. Robert West, Special Agent in the Office of Criminal Investigation at the Food and Drug Administration; Mr. Robert Ekey, Assistant to the Special Agent in Charge at the Special Investigations Division, Office of Inspector General at the Department of Housing and Urban Development—that's a long title—and Mr. Douglas Loveland, Special Agent in the Office of Criminal Investigation at the Food and Drug Administration.

Welcome, all.

It is the policy of this subcommittee to take all testimony under oath. Please be advised that witnesses have the right under the rules of the House to be advised by counsel during testimony.

Do any of you wish to be represented by counsel today?

All witnesses are indicating they do not.

Therefore, I am going to ask you to please rise and raise your right hand and take the oath.

[Witnesses sworn.]

Mr. STUPAK. Let the record reflect that the witnesses replied in the affirmative.

You are now under oath. We will now hear a 5-minute opening statement from this panel. You may submit a longer statement for the record. Your statement will be part of the record.

Mr. STUPAK. Ms. Cisneros, we will start with you, please, if you would.

**STATEMENT OF ANN MARIE CISNEROS, FORMER SENIOR
CLINICAL RESEARCH ASSOCIATE, PPD, INC.**

Ms. CISNEROS. Good morning, Mr. Chairman and members of the committee. I am honored that you are giving—

Mr. STUPAK. Would you pull that mike a little closer?

Ms. CISNEROS. Sure.

I am honored you are giving me the opportunity to tell my story.

My name is Ann Marie Cisneros. I am currently an independent clinical research associate. I served in the U.S. Air Force as a Medical Technologist, have a Bachelor of Science degree in Occupa-

tional Education, Wayland Baptist University, and an MBA from Pfeiffer University.

I have worked as a clinical research associate for approximately 8 years. My first 3 years in the industry I spent at PPDI, a contract research organization, where I monitored a number of protocols that included the large Ketek study, called Study 3014. At the time of the Study 3014, I was a senior clinical research associate and was tasked to assist with the monitoring of Dr. Ann Kirkman-Campbell's site.

Dr. Campbell is currently serving a 57-month prison sentence for fraud associated with Study 3014. In addition, she was ordered by the court to pay restitution to the drug sponsor Aventis, which had paid her \$400 per patient enrolled.

Mr. Chairman, based upon what I observed and learned in monitoring the Kirkman-Campbell site, Dr. Campbell indeed had engaged in fraud. But what the court that sentenced her did not know is that Aventis was not a victim of this fraud. On the contrary, let me explain.

Even before conducting the Kirkman-Campbell site visit, a number of red flags were apparent. I knew that Dr. Campbell had enrolled over 400 patients, or 1 percent of the adult population of Gadsden, Alabama. By comparison, another site in Gadsden had enrolled only 12 patients.

In a quality assurance audit by Aventis in early 2002, several informed consent issues were noted, as well as a significant under-reporting of adverse events and no reports of serious adverse events. No patients had withdrawn from the study, and no patients were lost to follow-up, an unusual occurrence given the number of subjects.

She enrolled patients within minutes of each other, and upwards of 30 a day. She enrolled patients at times and on days when her office was closed.

Once we started reviewing patient charts, we discovered that every informed consent had a discrepancy. Most of the consents looked like they had been initialed by someone other than the patient. A lot of the consents were dated by someone other than the subject. One consent was a blatant forgery.

There were date discrepancies as to when patients were enrolled in the study, had blood drawn, or had signed consent. Most patients diagnosed with bronchitis either had no history of the ailment or did not have a chronic condition.

She enrolled her entire staff in the study. Frankly, all Kirkman-Campbell seemed truly interested in was getting more business from Aventis as an investigator. At one point during my site visit, she told Aventis Project Manager Nadine Grethe that I could only stay if Nadine got her other studies at Aventis. Nadine must have agreed, because it is my understanding that when FDA audited the Kirkman-Campbell site, she was indeed participating in another Aventis clinical trial.

While at the site, I was so concerned about patient safety, I called Copernicus Independent Review Board or IRB to express my concerns and seek guidance. An IRB, which is under contract to the drug sponsor, has as its primary purpose patient advocacy. It is allowed to contact patients directly and is duty-bound to report to the

FDA any unanticipated problems involving risk to subjects and serious noncompliance with regulations.

I spoke with someone, who I understood to be the president of the company, and was told that while she shared my concerns, she preferred to wait and see what actions Aventis took. I never did hear from the IRB again, and to my knowledge, Copernicus never did audit or blacklist the site, or report any irregularities to the FDA.

I e-mailed a summary of my site visit findings to Robert McCormick, head of quality assurance at PPD, and copied Aventis personnel. I also participated in a teleconference between PPD and Aventis, at which I discussed issues identified in my site visit.

At some point after that, I understand that Aventis took site management responsibilities away from PPD because Dr. Campbell would not cooperate with anyone but the sponsor.

I subsequently left PPD, but learned that the Kirkman-Campbell site was being audited by the FDA. In preparation for the audit, I was told by a trusted and distressed former colleague at PPD that Nadine Grethe coached Dr. Campbell on how to explain away some of the site irregularities.

I was called on two occasions by PPD lawyers who reminded me of the confidentiality agreement I signed, and advised me not to speak with the FDA without Aventis approval and PPD attorneys present.

In my 8 years in clinical research work, this is the only instance I have come across of such abysmal behavior by a drug sponsor. I feel I can speak for those who agonized over the situation when I say we are pleased that Dr. Campbell is serving prison time for her actions, though what brings me here today is my disbelief in Aventis' statements that it did not suspect that fraud was being committed.

Mr. Chairman, I knew it. PPD knew it. And Aventis knew it. Thank you.

Mr. STUPAK. Thank you.

[The prepared statement of Ms. Cisneros follows:]

STATEMENT OF ANN MARIE CISNEROS

Good morning Mr. Chairman and members of the Committee. I am honored that you are giving me the opportunity to tell my story.

My name is Ann Marie Cisneros, I am currently an independent clinical research associate. I served in the United States Air Force as a Medical Technologist, have a Bachelors of Science Degree in Occupational Education from Wayland Baptist University and a Masters of Business Administration Degree from Pfeiffer University.

I have worked as a clinical research associate for approximately eight years. My first three years in this industry I spent at PPDI, a Contract Research Organization, where I monitored a number of protocols that included the large Ketek study called Study 3014. At the time of Study 3014, I was a senior clinical research associate and was tasked to assist with the monitoring of Dr. Anne Kirkman-Campbell's site.

Dr. Kirkman-Campbell is currently serving a 57-month prison sentence for fraud associated with Study 3014. In addition she was ordered by the court to pay restitution to the drug sponsor, Aventis, which had paid her \$400 per patient enrolled.

Mr. Chairman, based upon what I observed and learned in monitoring the Kirkman-Campbell site, Dr. Kirkman-Campbell indeed had engaged in fraud. But what the court that sentenced her did not know is that Aventis was not a victim of this fraud. On the contrary. Let me explain.

Even before conducting the Kirkman-Campbell site visit, a number of "red flags" were apparent. I knew that Dr. Kirkman-Campbell had enrolled over 400 patients

or 1% of the adult population of Gadsden, Alabama. (By comparison, another site in Gadsden had enrolled just twelve patients.) In a Quality Assurance audit by Aventis in early 2002 several Informed Consent issues were noted as well as a significant under-reporting of Adverse Events and no reports of Serious Adverse Events. No patients had withdrawn from the study and no patients were lost to follow up, an unusual occurrence given the number of subjects. She enrolled patients within minutes of each other and upwards of 30 patients per day. She enrolled patients at times and on days when the office was closed.

Once we started reviewing patient charts, we discovered that:

- Every informed consent had a discrepancy.
- Most of the consents looked like they had been initialed by someone other than the patient.
- A lot of the consents were dated by someone other than the subject.
- One consent was blatantly forged.
- There were date discrepancies as to when patients were enrolled in the study, had their blood drawn or signed their consent.
- Most patients diagnosed with bronchitis either had no history of the ailment or did not have a "chronic" condition.
- She enrolled her entire staff in the study.

Frankly, all Kirkman-Campbell seemed truly interested in was getting more business from Aventis as an investigator. At one point during my site visit, she told Aventis Project Manager Nadine Grethe that I could only stay if Nadine got her other studies at Aventis. Nadine must have agreed. It is my understanding that when the FDA audited the Kirkman-Campbell site, she was participating in another Aventis clinical trial.

While at the site, I was so concerned about patient safety I called Copernicus Independent Review Board or IRB to express my concerns and seek guidance. An IRB, which is under contract to the drug sponsor, has as its primary purpose patient advocacy. It is allowed to contact patients directly and is duty-bound to report to the FDA any unanticipated problems involving risks to subjects and serious non-compliance with regulations. I spoke with someone who I understood to be the president of the company and was told that, while she shared my concerns, she preferred to wait and see what actions Aventis took. I never heard from the IRB again. To my knowledge Copernicus never did audit or blacklist the site, or report any irregularities to the FDA.

I e-mailed a summary of my site visit findings to Robert McCormick, head of quality assurance at PPD, and copied Aventis personnel. I also participated in a teleconference between PPD and Aventis at which I discussed issues identified in my site visit. At some point after that I understand that Aventis took site management responsibilities away from PPD because Dr. Kirkman-Campbell would not cooperate with anyone but the sponsor.

I subsequently left PPD but learned that the Kirkman-Campbell site was being audited by the FDA. In preparation for the audit, I was told by a trusted and distressed former colleague at PPD that Nadine Grethe, Project Manager at Aventis coached Dr. Kirkman-Campbell on how to explain away some of the site irregularities.

I was called on two occasions by PPD lawyers who reminded me of the confidentiality agreement I signed and advised me not to speak with the FDA without Aventis approval and PPD attorney's present.

In my eight years in clinical research work, this is the only instance I've come across of such abysmal behavior by a drug sponsor. I feel I can speak for those who agonized over this situation when I say we are pleased that Dr. Kirkman-Campbell is serving prison time for her actions. But what brings me here today is my disbelief at Aventis's statements that it did not suspect that fraud was being committed. Mr. Chairman, I knew it, PPD knew it, and Aventis knew it.

Thank you for this opportunity to tell my story.

Mr. STUPAK. Do either of—the special agents, my understanding, do not want to make a statement.

Do you wish to say anything?

Mr. West.

Mr. WEST. Mr. Chairman, I don't have an opening statement.

Mr. STUPAK. Mr. Ekey?

Mr. EKEY. No, sir.

Mr. STUPAK. No, Mr. Loveland?

Mr. LOVELAND. No, sir.

Mr. STUPAK. OK, then we will go right to questions.

Ms. Cisneros, if I may, you indicated that after a couple days you called the IRB, Copernicus.

Ms. CISNEROS. Yes, sir.

Mr. STUPAK. Do you know when that was?

Ms. CISNEROS. It was probably 3 or 4 days into my visit, so either a Wednesday or a Thursday. I believe it was Wednesday of that week.

Mr. STUPAK. OK. Why did you call Copernicus?

Ms. CISNEROS. I knew fraud was being committed at the site, and I feared for patient safety. While I wanted to go up the chain of command at PPD, I just felt like Copernicus could take immediate action against the site.

Mr. STUPAK. Their responsibility is the patient safety?

Ms. CISNEROS. Correct.

Mr. STUPAK. Is that their main focus in a clinical trial, an IRB, institutional review board?

Ms. CISNEROS. Well, their main focus is approving informed consents and protocols that reflect patient safety, or to ensure patients are kept safe. But there was a statement in the informed consent that said the patients could call the IRB if they had any concerns.

Mr. STUPAK. Sure. So any concerns about patient safety should be directed to the IRB, then?

Ms. CISNEROS. Correct.

Now monitors aren't ever encouraged to call IRBs. There is just not a relationship there. So just to put that in the record.

Mr. STUPAK. So this was unusual for you to do this?

Ms. CISNEROS. Absolutely, yes.

Mr. STUPAK. But you felt compelled to call Copernicus?

Ms. CISNEROS. Yes.

Mr. STUPAK. How did you—by telephone, I take it?

Ms. CISNEROS. Yes.

Mr. STUPAK. Do you know who you called?

Ms. CISNEROS. I believe it was the president of the company at the time.

Mr. STUPAK. OK. Right in front of Mr. Ekey there, could you could hand her that big binder?

Would you please take a look at Exhibit No. 4?

Ms. CISNEROS. I am sorry, what number?

Mr. STUPAK. No. 4, please.

Ms. CISNEROS. All right.

Mr. STUPAK. OK. Exhibit 4 has two pages.

And while you are holding that tab, would you also go to Exhibit 33? I want to direct you to those two documents, 33 and 34—33 and No. 4, excuse me.

Could you identify number 33 for us?

Ms. CISNEROS. 33 is a telephone contact report taken by the IRB of my phone call.

Mr. STUPAK. OK. And it is dated February 21, 2002?

Ms. CISNEROS. Yes.

Mr. STUPAK. OK. This says IRB staff member taking call, Sarah Wallace.

Do you know who Sarah Wallace is.

Ms. CISNEROS. I don't recollect that name.

Mr. STUPAK. OK. Do you know if she is the president of Copernicus?

Ms. CISNEROS. To my knowledge, Sharon Hill Price was the president of Copernicus.

Mr. STUPAK. OK. Do you know Ms. Price?

Ms. CISNEROS. I do not, no.

Mr. STUPAK. OK. But it is your recollection that that's who you spoke to on that day?

Ms. CISNEROS. Yes.

Mr. STUPAK. OK. And does the—it says in here “she,” meaning you, has reviewed 50 of the 400 files, and some of her concerns are listed below. Do those accurately reflect your concerns?

Ms. CISNEROS. Yes, they do.

But I also remember saying that I was willing to furnish the IRB with patient names and phone numbers of patients I thought to be fraudulent in an effort to, again, have some validity as to whether these patients were actually true patients or not. I don't see that noted in this.

Mr. STUPAK. OK. Did the president of Copernicus then ask you for those names or numbers of these patients?

Ms. CISNEROS. No.

Mr. STUPAK. OK. Let me go to Exhibit No. 4, second page.

Again, would you please review the second page? Does that reflect any of the statements you may have made to Copernicus?

Ms. CISNEROS. I didn't go into detail about each subject. I pretty much said, every informed consent had an issue, and that one consent I believed to be a forgery. I didn't know what she was doing with the study drug, if patients were being given the drug and then not followed, that sort of thing.

So, no, I didn't go into specifics.

Mr. STUPAK. OK. On page 1 of that Exhibit 4, it says—it is from a Jessica Lasley—

Ms. CISNEROS. Uh-huh.

Mr. STUPAK [continuing]. And you are carbon-copied on this. And this was a telephone conference to discuss findings from monitoring of Kirkman-Campbell; is that correct?

Ms. CISNEROS. Yes.

Mr. STUPAK. This was a few days after you made the call on February 27, 2002?

Ms. CISNEROS. Yes.

Mr. STUPAK. Were you in on that conference call?

Ms. CISNEROS. Yes, I was, if it is the one—there was one teleconference that I was in on.

Mr. STUPAK. And do you believe this was the one then?

You are listed there as—carbon copy was sent to a Nadine Grethe and then carbon-copied to you.

Ms. CISNEROS. Yeah. This is an e-mail setting up the teleconference. So I participated in that teleconference, yeah.

Mr. STUPAK. Down at the bottom it says Ann Marie—that would be you?

Ms. CISNEROS. Yes.

Mr. STUPAK. And John have assembled some examples of this information we can share with you. Let us know. We have attached a summary of Ann Marie's findings during her visit.

Ms. CISNEROS. Correct.

Mr. STUPAK. OK. My time is up. I am going to want to come back to this witness. And let me just ask one question then, one more question.

Did Dr. Kirkman-Campbell react to you monitoring her site? Did she try to get rid of you during the course of your investigation.

Ms. CISNEROS. Well, she was very uncomfortable with us being there. She constantly complained about how we were taking up space in her office. She couldn't see as many patients as she wanted to, that sort of thing.

After—I believe it was Thursday of that week, she was going to send me home; and I was in her office, and she was on a teleconference—or she was talking to Nadine Grethe. And I heard her say, Nadine, I will let Ann Marie stay if you can get me into more Aventis studies.

Mr. STUPAK. So the Nadine that she was talking to was Nadine Grethe from Aventis?

Ms. CISNEROS. Correct.

Mr. STUPAK. And that is the same Nadine that is in Exhibit 4 that you had this telephone conference with on Wednesday, then, of that week that you were down there?

Ms. CISNEROS. Correct.

Mr. STUPAK. And the next day—on Thursday did you leave then, Dr. Kirkman-Campbell's office?

Ms. CISNEROS. I believe I left that day, yes.

Mr. STUPAK. Thank you.

Mr. WALDEN for questions then, please.

Mr. WALDEN. Thank you, Mr. Chairman.

Ms. Cisneros, you participated in that conference call with Aventis in March of 2002 to discuss concerns with Dr. Kirkman-Campbell's site, correct?

Ms. CISNEROS. Correct.

Mr. WALDEN. And what follow-up did Aventis decide to do to address PPD's concerns?

Ms. CISNEROS. Well, unfortunately, I left PPD shortly after that teleconference, so I am not quite sure what took place after that teleconference.

Mr. WALDEN. OK.

At the time of the call did you believe this follow-up was appropriate? But if you have left, then—

Ms. CISNEROS. No, I just remember from the teleconference how laissez-faire Aventis personnel were about the study findings and the excuses they provided for some of the oddities at the sites. It was very frustrating, because they didn't seem to want to acknowledge fraud in the least.

Mr. WALDEN. Do you believe Aventis intentionally ignored evidence of fraud? Or is it a matter that their processes and procedures for verifying fraud were faulty and couldn't have detected it?

Ms. CISNEROS. I personally believe they ignored evidence of fraud. You had to have your head stuck in the sand to have missed this.

Mr. WALDEN. Agent Loveland, if I could address a question to you—you may want to pull that mike fairly close—what do you think about their follow-up procedures?

Mr. LOVELAND. It is a catastrophic failure.

Mr. WALDEN. In what respect?

Mr. LOVELAND. The decision-making process that Aventis used to evaluate the warnings that Mrs. Cisneros and other PPD folks raised was illogical, ineffective. And it could have led them to not come to the proper conclusion; it was that bad.

Mr. WALDEN. Do you think that that process and procedure is in place and used in other drug evaluations? Have you seen any evidence of that?

Mr. LOVELAND. I don't know. I have seen other divisions of Aventis run clinical trials in other ways, and it was not this bad.

Mr. WALDEN. What makes this unique?

Mr. LOVELAND. From start to finish, their process for analyzing information coming out of the trial was poor.

When you get into a traffic accident, you call a traffic cop. These folks came in and they said, We have indicators of fraud, and they called a mathematician.

A mathematician didn't know what fraud looked like, and he couldn't identify it. He looked at all the data, couldn't figure out a rule to apply to the data set, came back and said, I don't see fraud. They took that to convince themselves that two of the most serious allegations raised by Ms. Cisneros and by other PPD folks weren't indicators of fraud.

The next thing they did was, they said, Well, let's take a look at all these uses of different-colored inks and the cross-outs and all the other things that teach us these are red flags when you see these in clinical trials. And they decided to fix them with a blizzard of memos to file that get filed with the IRB long after the patients were even enrolled.

Mr. WALDEN. Explain what you mean by that.

When you say "memos to file" and "a blizzard" of them, what were they saying in those memos?

Mr. LOVELAND. Essentially, that the monitors or the auditors had found these problems in each informed consent or in each medical record; the clinical investigator—in this case, Kirkman-Campbell—was reeducated or trained on how to do this right.

She signed the memo to file; and it was forwarded to the IRB, as though that had some sort of rehabilitative effect, and it didn't. In fact, the trial had stopped enrolling 2 months earlier. There is absolutely nothing the IRB could have done with them.

And the final serious allegation, which they held to the very end, that just fell off the radar—it was the allegation of forgery.

Mr. WALDEN. Have you found any evidence that this was intentional on Aventis' part? Or is it just sloppy? Or is it head-in-the-sand?

Mr. LOVELAND. It is interesting you would use the word "sloppy." That's how they described Kirkman-Campbell. And the problem is not so much that it is—was it fraud or was it sloppy. We want reliable data at the FDA.

Mr. WALDEN. Sure.

Mr. LOVELAND. Whether it is fraud or sloppy, it is not reliable.

Mr. WALDEN. Understood.

Mr. LOVELAND. Their threshold was, they had to find fraud. Before they would not submit it to the agency, which leads me to believe they were willing to submit sloppy data.

That is a flawed decision-making process.

Mr. WALDEN. At Aventis or at——

Mr. LOVELAND. At Aventis.

Mr. WALDEN. OK. If you suspected Aventis intentionally designed a system to not let itself know or be able to detect criminal fraud, what evidence would you seek to substantiate that suspicion?

Mr. LOVELAND. Well——

Mr. WALDEN. And was such evidence sought?

Mr. LOVELAND. Mr. West ran a great case with respect to Dr. Kirkman-Campbell.

Mr. WALDEN. Right.

Mr. LOVELAND. He proved in his investigation that falsified data was created.

Mr. WALDEN. Got it.

Mr. LOVELAND. Mr. Ekey did a great job during the 9 months he had the case of solidifying the complaint, making sure that he had all the complaining documents, that the data that were falsified were submitted to Aventis, and Aventis submitted them to the FDA.

So when I came in, all I had to do was figure out whether or not Aventis knew on the day they submitted the data that the data had been falsified. That was the only question left for me to answer.

Mr. WALDEN. And the answer was?

Mr. LOVELAND. I can't prove that beyond a reasonable doubt, and that's the standard I have to eventually meet in court. I only have one institution of resolution. It is the U.S. court system, and that is the standard I have to meet.

Unable to meet that, we refer it back to the FDA for regulatory action.

Mr. WALDEN. And you weren't able to meet that because of all the memos to file: that they had identified this, they had attributed it to a sloppy process, they reeducated the doctor, and so, therefore, because they admitted to all those things and had their memos to file——

Mr. LOVELAND. They actually took a number of steps. They had a meeting under their fraud SOP. They didn't do it very well, but they had one.

They had a plan. They didn't follow it real well, and the plan wasn't terribly effective, but they had one. They could individually answer every single allegation.

Collectively, you can look at it from 30,000 feet and show that it just didn't work, but they could individually answer each one. And what I described to you, sir, is more than reasonable doubt in the mind of a jury, and so at the end of the day, I would have failed in my only institution of resolution.

Mr. WALDEN. Could you briefly address the issue of debarment?

Mr. LOVELAND. No, sir. I don't know anything about it. That is a different part of the FDA.

Mr. WALDEN. All right.

Thank you, Mr. Chairman.

Mr. STUPAK. Thank you, Mr. Walden.

Mr. BURGESS for questions, please.

Dr. BURGESS. Thank you, Mr. Chairman. Let me ask any of the three investigators who would like to answer this: Is this an unusual situation? Have you investigated other companies for this type of allegation, and could you give us an idea as to how many companies have undergone such investigation?

Mr. WEST. Well, I can address what I have done in my 11 years. It is not normally the company that we are investigating; it is normally the PI who is conducting the clinical trial that we investigate.

Dr. BURGESS. So this was unusual in that it—

Mr. WEST. This is unusual, yes, in my experience.

Mr. LOVELAND. Those kinds of cases are actually handled by my unit. And this is not a very common type of an offense, where we have a major pharmaceutical corporation who has been accused of submitting intentionally falsified data.

That is not unheard of, but it is not terribly common.

Dr. BURGESS. But there have been other cases?

Mr. LOVELAND. I believe so.

Dr. BURGESS. And in those cases what did the fraud look like?

Mr. LOVELAND. The ones I am familiar with, it is dry-labbing, it is making up data.

In one case I ran a case where one company stole another company's data and submitted it. But these are not typically large companies like Aventis was.

Dr. BURGESS. So there is not really an established pattern that someone could rely on when a company—or when there is a suspicion that a company is involved; is that correct?

Mr. LOVELAND. This did not fit any pattern I have seen before, sir.

Dr. BURGESS. Then how did the company itself react to when you brought forth the issues that you have discussed with Mr. Walden?

Mr. LOVELAND. At the beginning of the week, they were very cooperative, very friendly, very warm, very hospitable. They pledged that they just had—they didn't believe it was fraud, they didn't see fraud during the conduct of the trial. They thought everything was OK, and they would be happy to make anything available to me that I wanted.

By the end of the week, they were saying, Gee, we have learned an awful lot here this week, because they sat in on all of the interviews.

Dr. BURGESS. So they learned a lot in the process of following you through your investigation?

Mr. LOVELAND. Well, they learned a lot that week, I believe.

Dr. BURGESS. Well, was the kind of fraud that took place with Dr. Kirkman-Campbell, was it unusual in your experience for the pattern of fraud in a clinical study?

Mr. LOVELAND. It is very typical type of PI-level fraud, making up patients. The only thing that was different here was, Kirkman-Campbell used actual patients with actual files. And in doing that, that does make it a little bit harder to detect, because when you

just completely make a patient up out of whole cloth there are some indicators in the patient's file that you can see——

Dr. BURGESS. But surely a big company like Aventis that is in the practice of doing these types of investigations, if there is a graphite titration, they should be able to pick that up, correct?

Mr. LOVELAND. They hire PPD to pick it up, and PPD picked it up. PPD sent signals to Aventis. They were loud signals, they were bright signals, and they were repetitive signals. Aventis should have known.

Dr. BURGESS. Well, in addition to the site that is under—that we are focusing on today, was there fraud at other sites as well?

Mr. LOVELAND. I believe there was.

Dr. BURGESS. Was that unusual, to find that there was this level of fraud at more than one site?

Mr. LOVELAND. No. When you have 1,826 “anybodies” put together, you are going to have an offender in the mix. You are going to have more than one offender. There are criminological studies out there that show this.

Dr. BURGESS. So this level was not unusual—or it was unusual?

Mr. LOVELAND. Eighteen hundred clinical investigators in one study is more than I have ever seen before. But what you have to have is a robust fraud detection and neutralization program to protect your clinical trial from the fraud and to preserve the sanctity of your data's integrity.

Dr. BURGESS. But could the company have anticipated this degree of misbehavior on the part of their investigators?

Mr. LOVELAND. They should have.

Dr. BURGESS. Do you think the level of fraud found in this Study 3014 is a function of having such a large study?

Mr. LOVELAND. That magnified it.

Dr. BURGESS. Was it the way in which the investigators themselves were selected?

Mr. LOVELAND. I am sorry, sir?

Dr. BURGESS. Did it in any way reflect on how the investigators were selected, how they were trained?

Mr. LOVELAND. I didn't look into that, and I wouldn't feel comfortable commenting on that.

Dr. BURGESS. In your opinion, would it be a lack of vigilance by the company in identifying and detecting fraud?

Mr. LOVELAND. Absolutely.

Dr. BURGESS. Do you believe that a company has to have absolute proof of fraud before it reports a fraud to the Food and Drug Administration?

Mr. LOVELAND. I don't. But again let's draw the distinction between what the FDA wants and what we are talking about here.

The FDA wants reliable data. And whether it is sloppy or fraudulent, that is not reliable. So fraud would be to the far end perhaps of unreliable data, but we don't want sloppy data either.

Dr. BURGESS. Right. So at that point, regardless of whether it is—whether you believe it to be fraudulent or just simply sloppy, what then is your obligation to report to the Food and Drug Administration?

Mr. LOVELAND. Well, I couldn't find an absolute written statutory obligation, but common sense says when you have this many indi-

cators, if you can't figure it out yourself, pick up the phone and call FDA. The doctors and the scientists that I interviewed at Aventis, they knew DSI's telephone number. They could have used it.

Dr. BURGESS. So the level of concern should have been to notify the FDA.

But you told Mr. Walden that you did not recommend that the FDA prosecute Aventis for fraud?

Mr. LOVELAND. I can't because I know that at the end of the day reasonable doubt exists, and I can't get that past a jury.

Dr. BURGESS. Do you think Aventis actually knew of this going on at these sites?

Mr. LOVELAND. They should have. If they didn't—

Dr. BURGESS. Knew it was sloppy or knew that it was intentionally fraudulent?

Mr. LOVELAND. Either one.

Dr. BURGESS. Either one.

Mr. LOVELAND. Well, they knew it was sloppy. They used "sloppy" as an excuse not to throw the fraud flag.

Dr. BURGESS. What prevented Aventis from acknowledging either sloppy or fraudulent? What caused them to stop short of saying this was a problem for us, too?

Mr. LOVELAND. The study director said that unless they had reasonable proof of fraud, the data were going to get submitted.

Dr. BURGESS. Thank you, Mr. Chairman. I will yield back.

Mr. STUPAK. We will be going another round, so we will continue questions.

Mr. Loveland, on page 5 of your report it indicates that you inspected five sites; is that correct?

Mr. LOVELAND. Sir, OCI does not do inspections.

Mr. STUPAK. It is on Exhibit No. 10 in the exhibit book there.

Ms. Cisneros, if you could give it to him.

We have your report there. And it looks like 19 or 11 sites you looked at.

Mr. LOVELAND. I am sorry, the tab was 10?

Mr. STUPAK. Yes, page 5 of your report. That is your report there, right, on page 10?

Mr. LOVELAND. That is correct, sir. These are actually paragraphs—I did not—for the record, I didn't go to any of these sites.

Mr. STUPAK. OK.

Mr. LOVELAND. These were actually removed from Aventis' own files.

Mr. STUPAK. So this page 5, these sites—Dr. Sarkar, Dr. Barber, Dr. Franklin, Dr. Sghiatti, Dr. Garner, Dr. Monticciolo, Dr. Jeffrey McCloud, Dr. Stone, Dr. Lang, Dr. Terpstra, and Dr. Ann Kirkman-Campbell—all that information about these sites then and the problems at these sites actually came from Aventis?

Mr. LOVELAND. That's correct. They had this knowledge. We didn't have it.

Mr. STUPAK. Right. And you included this in your report?

Mr. LOVELAND. Yes.

Mr. STUPAK. And in each one of these they are alleging problems and protocol violations which were significant enough to affect the integrity of the Study 3014?

Mr. LOVELAND. Data in it, yes, sir.

Mr. STUPAK. So Aventis definitely knew about—at least from 10 sites that there were significant problems.

Mr. LOVELAND. In actual fact, during one of the interviews, the interviewee told me that Aventis had 18 clinical investigators with whom they had significant GCP problems.

Mr. STUPAK. Associated with the Study 3014?

Mr. LOVELAND. That's correct. That is a 1 percent ratio. But some of these here are the highest enrolling sites.

Mr. STUPAK. So it is not just necessarily the number of sites, but also the number of patients enrolled at each site to make up your study, correct?

Mr. LOVELAND. That's correct.

Mr. STUPAK. And this is significant then, even this 1 percent of the sites?

Mr. LOVELAND. It was. And the reason I put it in the report is because it was—it explained the context of the data that were coming into the FDA from Aventis.

It wasn't just Kirkman-Campbell. The data were not reliable in other locations.

Mr. STUPAK. Did you reach the conclusion then that the data relied upon or the data relied on in 3014 was unreliable?

Mr. LOVELAND. I didn't have to. DSI did that. They get paid to make that decision, and I do not disagree with it.

Mr. STUPAK. OK. DSI?

Mr. LOVELAND. Division of Scientific Investigation is a division within the Center for Drug Evaluation and Research, and they actually schedule inspections. They actually read the reports and issue the instructions and all those sorts of things.

Mr. STUPAK. Very good.

Agent West, if I may, you opened a criminal investigation shortly after the FDA clinical site investigator, Ms. Smith, investigated Kirkman-Campbell's site; is that correct?

Mr. WEST. That's correct, sir.

Mr. STUPAK. And that was in October of 2002?

Mr. WEST. Yes, sir.

Mr. STUPAK. What did Kirkman-Campbell do when you notified her that you were conducting this criminal investigation?

Mr. WEST. When I approached Dr. Campbell at her clinic and asked to speak with her, the first thing that came out of her mouth was I will not speak with you unless I speak with Aventis personnel first.

Mr. STUPAK. Do you know if she spoke with Aventis?

Mr. WEST. I have no idea. But I'm assuming after I left she had to speak with Aventis because they had to prepare the 483.

Mr. STUPAK. And that's a—

Mr. WEST. That's the response to the inspection.

Mr. STUPAK. OK. So Kirkman-Campbell had to file this report in response to your inspection?

Mr. WEST. It's a response to the regulatory inspection, not my criminal case.

Mr. STUPAK. Why were you convinced Aventis should be criminally investigated for knowledge of Study 3014?

Mr. WEST. My feeling at the time was based on what I was observing, not only in Kirkman-Campbell's clinical trial, but also my

interviews of PPD personnel, along with Aventis personnel. And I felt at the time that it was sort of like blatant disregard for information that they were receiving from the field and providing to the FDA.

Mr. STUPAK. Do you still feel that today?

Mr. WEST. Yes, sir.

Mr. STUPAK. I understand that Dr. Kirkman-Campbell was the drug company sales representative to supply blood for the Ketek study, is that correct?

Mr. WEST. That's correct.

Mr. STUPAK. Should the drug company representatives have known what the blood was being used for?

Mr. WEST. Oh, I think they knew that Kirkman-Campbell was conducting a clinical trial. What they told me was that they were just going to allow her to use their name in a clinical trial so that they could continue to have her business as a pharmaceutical rep.

Mr. STUPAK. By "they," you mean the blood company representatives or Aventis?

Mr. WEST. The company that each one of the pharmaceutical reps were representing at the time.

Mr. STUPAK. In the course of your investigation, did Dr. Kirkman-Campbell, did you learn that Aventis had flown her to California to teach, so she could teach other people how to do these clinical trials?

Mr. WEST. Based on what she told us is that, yes, Aventis flew her out to California so she could teach other PIs how to conduct clinical trials.

Mr. STUPAK. PI being principal investigators?

Mr. WEST. Principal investigators.

Mr. STUPAK. To your knowledge, did Kirkman-Campbell do another study with Aventis?

Mr. WEST. I think when I was there conducting my criminal case, not only was she conducting studies for Aventis, but she was conducting studies for GSK GlaxoSmithKline.

Mr. STUPAK. Would you please take a look at the exhibit book, Exhibit Number 25, if you would. Could you identify what that exhibit is?

Mr. WEST. This looks like an e-mail from Dr. Campbell to a member of Aventis basically saying thanks for assisting me in preparing the 483.

Mr. STUPAK. And that is thanking Aventis for helping her fill out forms for another study, is that correct?

Mr. WEST. That is correct.

Mr. STUPAK. And that e-mail is dated November 17, 2002, is that correct?

Mr. WEST. That is correct.

Mr. STUPAK. Were you doing your criminal investigation of Dr. Kirkman-Campbell on Ketek at that time?

Mr. WEST. Yes.

Mr. STUPAK. Turn to Exhibit Number 8 if you would, please.

Mr. WEST. Did you say 8?

Mr. STUPAK. Eight, yes. In this memo, you're recommending that the investigation should be undertaken by the FDA into whether

Aventis knew that Study 3014 contained fraudulent data when it was submitted to the FDA. Is that what that is about?

Mr. WEST. That is correct.

Mr. STUPAK. And who are you doing this study to in the FDA? Or, I'm sorry, your recommendation?

Mr. WEST. In this particular e-mail, I was responding to Director Vermillion, who is the director of OCI. But the e-mail is in response to a conversation I had with CDER personnel, Dr. Solif, Dr. Goldberger, Dr. Cox and Dr.—well, this particular e-mail was just with those three individuals.

Mr. STUPAK. When you say CDER, that's Center for Drug Evaluation and Research, right?

Mr. WEST. That's correct.

Mr. STUPAK. And you were trying to get them to allow you to continue the investigation into Aventis whether or not Aventis knew the fraud before they submitted 3014 to the FDA, correct?

Mr. WEST. That's correct.

Mr. STUPAK. And what happened as the result of your conversations with officials at CDER?

Mr. WEST. Well, first of all I have to say that the reason why I needed CDER support is that I don't have the authority to go out and conduct inspections on PIs. I needed DSI to issue assignments to the regulatory so they could go out and do inspections. That's what I was recommending to Goldberger, Solif and Cox. And I did not hear anything, I did not get a response from them. But I heard through the grapevine that they declined to participate because of personnel problems and money.

Mr. STUPAK. Would it be a huge financial commitment of resources or money to do this investigation?

Mr. WEST. No, because I was only asking for their support. In other words, provide assignments to regulatory to go out and actually conduct the inspections. OCI and other regulatory inspectors would have actually conducted the review of documents.

Mr. STUPAK. And in this Exhibit Number 8, you basically lay out how you would do it, correct?

Mr. WEST. That's correct.

Mr. STUPAK. How you would go about it. If you had this opportunity, you would go out and do this investigation and you were willing to go do it?

Mr. WEST. That's correct.

Mr. STUPAK. Did you believe there was a possibility of detecting fraud if they just followed your recommendations as you laid out in Exhibit Number 8?

Mr. WEST. Oh, I believe that we would have detected fraud in other sites.

Mr. STUPAK. In your opinion, did someone at CDER, the Center for Drug Evaluation and Research at the FDA or elsewhere in the FDA block your proposal to create this task force to go look to criminally investigate Aventis in connection with Study 3014?

Mr. WEST. I believe someone above the individual that I was speaking to, which was Brenda Friend, blocked the participation of the center to support OCI.

Mr. STUPAK. Do you have any idea who that individual would have been?

Mr. WEST. I have no idea.

Mr. STUPAK. Is it possible that because of the failure to investigate, Aventis personnel and others may have committed criminal violations of the Food and Drug and Cosmetic Act without being charged?

Mr. WEST. Oh, most definitely.

Mr. STUPAK. Did you ever talk to the Dr. Kweder from the FDA?

Mr. WEST. Yes, I spoke with Dr. Kweder. I briefed her the same way I briefed Goldberger, Solif and Cox. I also provided her with the same recommendations. And I also explained to every one of them that we couldn't, as OCI we couldn't demand, because there was legal issues. If we demand them to do something and they go out and do it, then we're sort of conducting a search which would have created a legal issue for us. So we recommended or suggested that they go out and do further inspections, which they declined.

Mr. STUPAK. So besides Exhibit Number 8, this e-mail, you had other conversations with Dr. Kweder, Cox and others about where this investigation should go, in your recommendation it should continue to look at what Aventis knew prior to submitting this data to the FDA in Study 3014?

Mr. WEST. Oh, yes. Not only those individuals, but I was in constant contact with DSI explaining to them what was going on in the criminal case so they could be aware because of 3014 being submitted and up for approval.

Mr. STUPAK. Thank you. Mr. Ekey, we haven't asked you any questions. Do you have anything you would like to add?

Mr. EKEY. I'll wait until you have a question. Thank you.

Mr. STUPAK. OK. Mr. Walden.

Mr. WALDEN. Thank you very much, Mr. Chairman. Mr. West, I want to follow up this notion about Dr. Campbell. You obviously found problems with her work in the Aventis case. I'm hearing for the first time she was involved in other trials, which I guess shouldn't be a surprise. Has anybody gone back to look at her work in those other cases?

Mr. WEST. We did.

Mr. WALDEN. And did you find any instances of—

Mr. WEST. She was conducting a study for GSK. I can't remember the drug. But it was for migraines.

Mr. WALDEN. OK.

Mr. WEST. And I think it was a post market study. And we determined just by reviewing three or four records, which were provided to us by GSK, that they were fraud. And we provided that information to GSK and to DSI. We were not going to incorporate that in the criminal prosecution because we had enough on her regarding 3014, the Ketek study. But I made sure that both GSK and DSI were aware that we had proven that she committed fraud in the migraine study because she enrolled the same pharmaceutical reps in the migraine study. And we talked to them and they said, well, I didn't have the symptoms, I was just participating because she asked me to.

Mr. WALDEN. That was the phase 4 four-person Lantis study?

Mr. WEST. I'm not quite sure. All I remember was the migraine.

Mr. WALDEN. Do you know how big a study that was? The one we're dealing with here with Aventis was what 12,000, 24,000 peo-

ple, 12 on a placebo, 12 not, and that was extraordinarily large. Do you know on the GSK study on migraine medicine?

Mr. WEST. I believe that was a relatively small study.

Mr. WALDEN. What would that be? Give me a number.

Mr. WEST. I know for a fact that Campbell only had I think 12 or 15 enrollees.

Mr. WALDEN. Ms. Cisneros, do you know anything about that one?

Ms. CISNEROS. I do. Actually, when I was at Dr. Campbell's site, she had me make 50 copies of an informed consent for the GSK study. I had a colleague that worked at GSK in the neuro division that I made aware of the study. And to my knowledge, the study manager from GSK, as well as it was actually a PPD study as well, went out and auditing Campbell's site and didn't find any issues.

Mr. WALDEN. Didn't find any issues? But Mr. West, you said you found obvious fraudulent issues. Do you want to pull that mike back over your direction. What's going on here?

Mr. WEST. Well, I can tell you that Investigator Patty Smith and myself, we both reviewed records that were provided to us by GSK, and it was quite obvious that Campbell was committing fraud on that particular study.

Mr. WALDEN. Do you know if GSK excluded her data from that?

Mr. WEST. I have no idea. I provided the information to GSK and to DSI.

Mr. WALDEN. Has that drug been approved, whatever it was?

Mr. WEST. Well, it was already approved for one indication. I think this was a post market for an off label use?

Mr. WALDEN. Do you know if that process has made its way through the system? Does anybody know?

Mr. WEST. No.

Mr. WALDEN. It just obviously troubles me that we seem to have the same doctor engaged in the similar sort of conduct allegedly involving yet another drug. And Ms. Cisneros, you indicate you were aware of this and made somebody else aware of this?

Ms. CISNEROS. I did.

Mr. WALDEN. And they disagree?

Ms. CISNEROS. Well, they didn't have to report back to me, so I don't know what the outcome was.

Mr. WALDEN. Who did you make aware of this?

Ms. CISNEROS. I would rather not say her name, but a colleague that worked at GSK in that division that was marketing that drug.

Mr. WALDEN. Well, Mr. Chairman, we may want to find out who that person was.

Ms. CISNEROS. OK. Off the record.

Mr. STUPAK. Ms. Cisneros has been forthcoming in all matters. If she wishes to tell us privately, since we don't have an active investigation, maybe we should because we've uncovered some other stuff in working on this that there may be further investigations. So we'll get that information.

Mr. WALDEN. Thank you, Mr. Chairman.

Mr. STUPAK. We certainly plan on following it up.

Mr. WALDEN. Mr. Loveland, why do you believe it took almost 5 years after the Study 3014 was submitted by Aventis for FDA to

open an investigation of the company and its knowledge of fraud? Why did it take 5 years?

Mr. LOVELAND. Because for the first 3 years following Mr. West's investigation throughout her indictment and her presentencing period all the way through her sentence, all the way through her appeals Kirkman-Campbell was convicted of defrauding Aventis. She never came forward and said Aventis knew also until the night of March 2, 2006. She had contacted Mr. West some time earlier that week or within a week or so. Mr. West went to the prison, interviewed her and sent an e-mail the following morning to my unit. The head of my unit at that time was Kathy Martin-Weis. And within an hour, that had been forwarded to Mr. Ekey and the case was undertaken.

Mr. WALDEN. So nothing started from your perspective until Dr. Campbell?

Mr. LOVELAND. We didn't have a complaint that Aventis knew about it.

Mr. WALDEN. So there wasn't an effort not to investigate?

Mr. LOVELAND. Right.

Mr. WALDEN. You had no reason to investigate?

Mr. LOVELAND. It never came to our office as a complaint.

Mr. WALDEN. I see. Do you think it should have? Was there anything, Mr. West, that you found in the course of prosecuting or doing the investigation of Dr. Campbell that should have triggered somebody to look at Aventis?

Mr. WEST. Well, we tried to get the support from the center. But in 2004, the drug was approved and we were involved with the Campbell prosecution.

Mr. WALDEN. How many of these sorts of investigations do you undertake at a given time? What kind of caseload are we talking about here?

Mr. WEST. Do you mean clinical trial investigations or all total?

Mr. WALDEN. Give me a total.

Mr. WEST. I probably am working right now on 15 criminal cases. And OCI cases are not "wham bam thank you ma'am." They go on for 2 or 3 years, sometimes 4 years, sometimes 5. And they're very paper intense, so.

Mr. WALDEN. All right. Mr. Ekey, how about you?

Mr. EKEY. Yes, sir.

Mr. WALDEN. The number of cases you're working on right now?

Mr. EKEY. The group I was assigned to was the special prosecution staff which handled allegations on larger pharmaceuticals, so our caseload was lighter. We carried perhaps six, seven cases.

Mr. WALDEN. All right. Mr. Loveland.

Mr. LOVELAND. I currently have six cases, two or three of which are clinical trials.

Mr. WALDEN. What kind of fraud training do you think pharmaceutical companies should provide to their employees? Do you think it's adequate? What should it be? How do we prevent this from happening again? What do we need to do?

Mr. LOVELAND. It wasn't adequate in this case. I know of other companies that have very robust training programs and they manage to keep their clinical trials fairly fraud free.

Mr. WALDEN. But as we look at the number of sites, I think, what, were there 1,800 sites in this 2014 study? And each doctor got paid, what, \$100 for every person they signed up?

Mr. LOVELAND. \$400 for each randomization. And that's a very low number typically.

Mr. WALDEN. Really?

Mr. LOVELAND. Very, very small.

Mr. WALDEN. So it's sort of like getting somebody's debit card and every time you sign somebody up you get another \$400 withdrawal?

Mr. LOVELAND. Interestingly, in this case, that's part of what made this fraud work. Aventis uses the IVRS system to do basic data collection and drug randomization in many of its trials. It's a great system. It's a very good tool for capturing study data. What most people don't know is that when you hang up the phone, it also sends a message over to accounting in finance and says send this doctor another \$400 because they just randomized another patient.

So what Kirkman-Campbell was doing, actually every 50 to 70 seconds, was printing a new \$400 bill, and it would get mailed to her at the end of every month. Think about an ATM machine, and that's how the system works. The system is actually constructed to have fraud indicators built in. And those fraud indicators were tripping. And PPD picked them up and PPD provided them to Aventis. And this is one of the two analyses that the mathematician did, not knowing that what he was looking at was a fraud indicator log.

Mr. WALDEN. He didn't know that?

Mr. LOVELAND. He didn't know it.

Mr. WALDEN. Where did he think it came from then?

Mr. LOVELAND. Well, it's an administrative printout. It looks much like a telephone bill.

Mr. WALDEN. So what did he think, it was like the button stuck down?

Mr. LOVELAND. No. What he decided it was is that this lady was very adept at using the IVRS system.

Mr. WALDEN. I would say so. I was a journalism major, not a math major, but I can figure that one out.

Mr. LOVELAND. OK. And the story he got was that this particular clinical investigator would see 10, 12 patients, agreed to enroll them and then on her time off or on her lunch hour or on her day that she was closed and doing office work she would sit and randomize them all.

Well, if you take the protocol and you read the protocol, you know you can't do that. And one of the things that troubled me with the decision-making process is when I asked the management about that. They said, well, that's a plausible answer, it may not be a good practice of medicine, but it's a plausible answer, which immediately begs the question: Do you want not such a good practice of medicine in your clinical trial?

Mr. WALDEN. Right. And it seemed like from the one tab I was reading, I think the chairman referenced, I don't remember the exact page number or tab, but the problem with Dr. Campbell wasn't unique—I mean, it may have been unique in that she's in jail and did fraudulent activity, but it seemed like there were a lot of discrepancies in multiple locations, is that correct?

Mr. LOVELAND. I believe I was told by one member of management that there were problems with virtually every informed consent form, because doctors don't tend to do those in the course of—in the normal practice of medicine.

Mr. WALDEN. Right. But they're not in the normal practice of medicine if they've agreed to participate in a clinical trial, are they?

Mr. LOVELAND. That was one of the conflicts that was set forth in this whole case. One of the conflicts in this case was a large simple safety study, to my understanding, is typically done post marketing, not to good clinical practice standards. Every Phase III trial has to meet good clinical practice standards or the perception is the FDA will not accept the trial. So here we took a methodology that's typically used apparently in Phase IV, not to good clinical practices and we moved it into Phase III. Everybody has looked at that and said, OK, that's probably the last time we're going to do that, it just didn't work.

Mr. WALDEN. All right. Thank you. Thank you, Mr. Chairman, for your indulgence on the time too.

Mr. STUPAK. Sure, Mr. Walden. Mr. West, you may or may not know this. You talked about the migraine study. You said you notified DSI. That's the Department of Scientific—

Mr. WEST. The Division of Scientific Investigations.

Mr. STUPAK. That's within FDA?

Mr. WEST. That's correct. Within the Center for Drugs.

Mr. STUPAK. Right. CDER, Center for Drug Evaluation and Research?

Mr. WEST. That's correct.

Mr. STUPAK. So FDA and the people responsible for making sure that drugs are safe and the approval of drugs, they knew not only about Aventis, but also about this migraine study that you mention?

Mr. WEST. That's correct.

Mr. STUPAK. And I had asked you about Exhibit Number 25, which is actually where she faked Aventis, that's my understanding actually, a diet pill. So those are at least three different. Do we know of any other studies that during this time frame 2002–2003 Dr. Kirkman-Campbell was involved with? We know of at least three. Do we know of any others?

Mr. WEST. No, sir.

Mr. STUPAK. Ms. Cisneros, do you know?

Ms. CISNEROS. No.

Mr. STUPAK. Mr. Ekey do you know of any other studies of Dr. Kirkman-Campbell? Or Mr. Loveland?

Mr. EKEY. No, sir.

Mr. LOVELAND. No, sir.

Mr. STUPAK. Mr. Loveland, in your belated interview with the committee last Friday, you summarized your findings regarding Aventis' complicity in Study 3014 clinical fraud as follows, and I'm quoting now, "Aventis should have known of the fraud. And if they really were unsure they should have contacted the FDA for assistance in substantiating the fraud." Is that true?

Mr. LOVELAND. Yes.

Mr. STUPAK. In a timeframe, 2002–2003, what would Aventis have known or what red flags were they aware of to make you make that statement?

Mr. LOVELAND. During the period of time that the trial was enrolling, they probably did not know very much. There was one monitoring trip very early and they showed some small sloppiness things that could adequately be dealt with memos to file and some training. There was one auditing trip that was a catastrophe. The poor auditor, it was his first trip, he just joined the company, he walked in the door and expecting 100 or so patients found 360. He spent literally the entire 2 days going over informed consents. He never got to data in any meaningful fashion.

Mr. STUPAK. And this auditor was an Aventis employee?

Mr. LOVELAND. That's correct.

Mr. STUPAK. In what timeframe was that?

Mr. LOVELAND. That was mid-January of 2002.

Mr. STUPAK. OK.

Mr. LOVELAND. In fact, it was January 22nd. He exited the place feeling uncomfortable and he reported to the study team, I'm not terribly comfortable with this site.

Mr. STUPAK. The study team being the Aventis study team?

Mr. LOVELAND. That's correct. We need to increase the monitoring, we need to increase the source data verification, and we need to take a look at maybe some more training. But the trial was moving along so quickly that enrollment ended by January 30th so new people came in—or stopped coming in just a few days later.

Mr. STUPAK. So even at the beginning of this study Aventis had red flags or warnings that things weren't even starting off on the right foot?

Mr. LOVELAND. I read that monitoring report. That did not look like a huge red flag. The first really serious sets of red flags started coming up with Ms. Cisneros' visit. And during my investigation, I made it a point to go back and visit with her again and collect what is typically known as a smoking gun document, that document which she forwarded to Aventis, because that imputed more knowledge to Aventis than any other document in the case.

Mr. STUPAK. That document, you mean the record of her phone call that we had cited earlier in this hearing?

Mr. LOVELAND. She actually typed up a memo. Perhaps it was.

Mr. STUPAK. OK. It would be Exhibit Number 4, I think we talked about.

Ms. CISNEROS. I believe he's talking about the forged document.

Mr. LOVELAND. No. Your list of all the patients.

Mr. STUPAK. Exhibit Number 4, I think we talked about. So that was the smoking gun that Aventis should have known and went there then?

Mr. LOVELAND. That was the document, the teleconference.

Mr. STUPAK. And that was in 2002?

Mr. LOVELAND. That's correct.

Mr. STUPAK. And Ketek was approved in 2004. So two years before it was even approved Aventis knew?

Mr. LOVELAND. Oh, sure. But this is even before Aventis submitted the data. So contemporaneously with the March 4th telephone conversation, some other folks at PPD sent some data up to

Aventis saying there's some problems here as well. And then on the 6th of March some more data came up saying there's problems with these new forms.

Mr. STUPAK. And this is all 2002.

Mr. LOVELAND. That's correct. So the period of time my investigation focused upon was from that period through the 23rd of July, because it was the 23rd of July that they submitted the data to the FDA. So during that period of time were they capable of learning that the data had been falsified? Well, employing the decision-making process that they did, they contend they never discovered the falsity of it.

Mr. STUPAK. So there's no doubt in your mind that Aventis knew before they submitted 3014 that there were major problems with the integrity of the data to support their conclusions that Ketek was safe based on Study 3014?

Mr. LOVELAND. I'll accept that wording. They contend they didn't know it was fraudulent. But I'll accept what you said.

Mr. STUPAK. But there's no way they would not know unless they just turned a blind eye to everything?

Mr. LOVELAND. If you take a mathematical analysis and you take the first allegation and you say the first allegation is disproven, you take a mathematical analysis and you take that second allegation and the mathematical analysis disproves it, OK, that one is not true, I'm now down to sloppy and a forgery. We can fix sloppy with the memos to file and if the forgery falls off the radar I'm describing a fairly incompetent system here.

Mr. STUPAK. Sure. Mr. West—excuse me one minute. I just want to go back to Agent Loveland. I want to ask you one more question. Tab number 14, if you take a moment, please, sir. Tab 14 is two pages. It looks like an e-mail you're receiving dated Wednesday, April 14, 2007, and then Tuesday, April 17, 2007.

Mr. LOVELAND. Where would you like me to go, sir?

Mr. STUPAK. The second page, last paragraph. Could you explain that? I think this is from you to Ian Walsh. In Ketek new drug application, the sponsor clearly sent falsified data on Study 3014?

Mr. LOVELAND. Right.

Mr. STUPAK. Explain that for us. Aventis knew that such significant issues existed. It had so many sites that the GCP—what is that, GCP, what does that mean?

Mr. LOVELAND. Good clinical practices. It's a standard, sir.

Mr. STUPAK. Right. Could not be claimed, yet it claimed a study was conducted to good clinical practice, GCP. Think—now, these are your words, right?

Mr. LOVELAND. That's correct.

Mr. STUPAK. Think, "willful blindness," on steroids, but they submitted anyway. What do you mean by willful blindness on steroids?

Mr. LOVELAND. I had never seen, except in a trial conducted out of Florida, that was intentionally falsified, we put them in prison, I had never seen such a significant number of GCP issues. You referenced it earlier in the questioning, sir, when you took me to page 4 of my first RRI, there's 11 different sites that they themselves wrote up. And during the interview——

Mr. STUPAK. "They themselves," you mean Aventis wrote up?

Mr. LOVELAND. That's correct. And then in the interview, one of the managers said we had 18 folks with significant GCP issues. If you had 18 sites with significant GCP issues, why did you submit their data?

Mr. STUPAK. Correct. I guess that will be for the Aventis panel. Let me ask you this, Mr. West. Since it appears you dealt with the FDA—wait for these buzzers. Let me ask you this. Since you dealt with the FDA, CDER, Center for Drug Evaluation and Research, and also the DSI, Division of Scientific Investigations, within the FDA, before Ketek was approved in 2004, is there any doubt in your mind that they knew there was fraud with Study 3014? By they, I mean the FDA officials.

Mr. WEST. Oh, I had conversations with Brenda Friend many times. And she agreed with my recommendation that we needed to move forward because of the fact that it appeared that 3014 was just riddled with fraud.

Mr. STUPAK. And she kicked it upstairs to CDER?

Mr. WEST. She must have kicked it up to somebody, because she just—I think she works the ground level of DSI, so she had to kick my recommendation above her, and the people above her must have declined.

Mr. STUPAK. Let me ask you this. In your opinion, has the statute of limitations run on the possibility of indicting Aventis for fraud in connection with Study 3014?

Mr. LOVELAND. If I may, sir, that would be my case.

Mr. STUPAK. OK.

Mr. LOVELAND. And the answer is yes the statute of limitations has run with 3014. They submitted the data on July 23, 2002. It's got five years. If I could find a law that went farther, I would use it. If I could have found a strict liability statute, I would have pushed for that. But I only had 1001, it's 6 on the guidelines, it's all I can do, that's run, I can't go back to it.

Mr. STUPAK. OK. If Ketek is used for one of the, being used for three different; bronchitis, sinusitis and pneumonia, now it's only supposed to be used for community-based pneumonia, if after July of 2002, it's prescribed for bronchitis, contrary to what it's supposed to be now, would that reinvigorate the statute of limitations? Would the statute of limitations start to run from the time it's prescribed since its approval was based on 3014?

Mr. LOVELAND. I'm not a lawyer and I'm not going to go there, but I don't believe so. The only thing that I'm aware of that would allow us to take the statute beyond would be a subsequent affirmative step in the commission of a conspiracy. And we use that to lengthen the statute of limitations. I didn't have that here.

Mr. STUPAK. OK. If it was submitted in '04, if Study 3014 was submitted—

Mr. LOVELAND. My statute of limitations would run next year.

Mr. STUPAK. Right. So if they submitted the study, Aventis submitted the Study to the FDA, Study 3014, in 2004 for approval of this drug, the safety indicators, would not your 5 years run from '04 then?

Mr. LOVELAND. '04 to '09, correct.

Mr. STUPAK. So you still have a statute of limitations opportunity then for the possibility of indicting Aventis for fraud in connection

with Study 3014 knowingly submitting a fraudulent study to the FDA?

Mr. LOVELAND. 3014 was submitted to the FDA in July of '02, sir.

Mr. STUPAK. Right. But it wasn't approved until '04, was it not?

Mr. LOVELAND. I don't know that that—I'm not—I can't go there. I don't know what that ties.

Mr. STUPAK. Sure. OK. Mr. Ekey, I don't want to leave you out, and I said I would ask you one.

Mr. EKEY. Thank you, sir.

Mr. STUPAK. I want to read you a short segment. And I don't want to leave you out because the work all four of you have done and the willingness to come forward and testify, even though it was under subpoena, has been a great help to this committee, in the institutional review boards and CROs, all the things we're looking at, so we certainly do appreciate all you've done and we take great stock in what you say.

So let me just ask you this, because I just want to ask the statement that you read in your report. A short segment from the last page of your report. It's Exhibit Number 9 in the book, if you care to look at it. The reporting special agent, that would be you, believes that the testimony and documentary evidence indicate that Aventis was well aware of serious data integrity problems at the Kirkman-Campbell site, yet submitted this data to the FDA. When questioned by the FDA review committee Aventis stated they had knowledge of problems but did not explain why this data wasn't excluded from their submission, nor did they explain why they didn't notify the FDA. Additionally, Aventis falsely claimed to have stopped enrollment at the Kirkman-Campbell site. So is it fair to say, based on that statement, that you came to believe that Aventis was aware of serious data irregularities when they submitted the data to the FDA?

Mr. EKEY. I believe so, sir. I believe documents and interviews show that key Aventis personnel did know that there was serious integrity problems at that site.

Mr. STUPAK. You also indicate the last line, "Aventis falsely claimed to have stopped enrollment at the Kirkman-Campbell site." Explain that last paragraph. So even after they knew it, they continued to have Dr. Kirkman enroll patients?

Mr. EKEY. Just for a little back story, I did leave the FDA in January of '07, so I'm doing a lot of this without the benefit of notes, documents like that. My recollection is that is information I obtained from FDA doctors that were on that committee. That's the best of my recollection. I don't have that document.

Mr. STUPAK. Doctors on that committee?

Mr. EKEY. I believe it was Dr. Ross.

Mr. STUPAK. OK. Would that be the advisory committee to the FDA that received the information?

Mr. EKEY. Yes.

Mr. STUPAK. Thank you. I have no further questions. And again, thanks to this panel. Mr. Inslee, thanks for getting here. I know at the early start, flights and all that, thanks for being here. Do you have any questions?

Mr. INSLEE. I do. Thank you. Just for the whole panel, I've been looking at this issue of fraudulent medical devices, alleged medical devices, that are used to take advantage of people who are in distress. And a local newspaper in Seattle has done some really good work looking at how many of these devices are now marketed to people who are in desperate situations. A lot of these electrical devices that have screens and sparks and everything else, but no medical validity. And one of the ways that folks have been able to do this is by using these independent review boards to sort of purport to be in some trial when they're really just scams of the darkest dimension.

I just want to ask you if you have any thoughts about these institutional review boards and how they are working or should work or may or may not be able to use to really cover up things that are not medically appropriate? Just looking for your advice. That's an open question to any of you. Looking for free advice.

Mr. LOVELAND. Sir, this really is not OCI's bailiwick.

Mr. INSLEE. I hear you. We'll take advice from anywhere in America, though. We're sort of an open review concept. Well, with that I'm going to thank you for your testimony. Thanks, Mr. Chairman.

Mr. WALDEN. [Presiding.] You're welcome, Mr. Inslee, and it's great to be back in the Chair, if only by accident and for a very short period. I just have one question, Mr. Loveland, because you talked about statute of limitations and all that. It seems to me that there's a disconnect in the FDA statutes. Are you familiar with the 331q for medical device prosecution?

Mr. LOVELAND. Yes.

Mr. WALDEN. So if it was a medical device issue you could still pursue that under a different standard, correct, than drug issues? You could file a false statement and prosecute under a misdemeanor statute?

Mr. LOVELAND. Well, 21 U.S.C. 331(q)(2) makes it a prohibited act to make a materially false statement to the FDA in any matter—in a required report in a matter involving a medical device.

Mr. WALDEN. Right.

Mr. LOVELAND. There is no similar statute for a drug, a food, a biologic or anything to regulate.

Mr. WALDEN. Why is that?

Mr. LOVELAND. I don't know, sir. I thought laws come from you folks, not from us.

Mr. WALDEN. The good ones do. Obviously, I'm feeling a new one coming on.

Mr. LOVELAND. Let's not make any new laws, just erase the last few words.

Mr. WALDEN. Well, that takes a law to do that.

Mr. LOVELAND. Instead of making it medical devices only, let's make it a prohibited act to make a false statement to the FDA in any required report. Now, the beauty of the FDNC Act is that at the misdemeanor level it's a strict liability statute. And in a case like this what the prosecutor and I discussed was sending a message to industry and what is the best way to do this. We can't prosecute because the facts just aren't there that will support a criminal prosecution at 18 U.S.C. 1001, which is the typical false state-

ment statute. When we discussed that had, in fact, 331(q)(2) not been limited to medical devices, I would very much have been advocating to send a strict liability misdemeanor. And misdemeanors are not fun to prosecute. They take up a lot of time and they're typically thought to——

Mr. WALDEN. But it does give you a hammer.

Mr. LOVELAND. But it would have sent a message to industry that you are responsible for your data, all of them. You have to protect your clinical trials and you have to protect the sanctity of your data. It just wasn't available to us.

Mr. WALDEN. It would seem to me if it is good enough for a medical device, it should especially be good enough as another tool for you to use for the safety of our food and drugs.

Mr. LOVELAND. I would have liked to have it that day, sir.

Mr. WALDEN. All right. Thank you. I don't think we have any other witnesses. I'll let the chairman make that decision, though.

Mr. STUPAK [presiding]. Again, let me thank this panel and thank you very much for being here and thank you for your work. We'll call our third panel. Senator Grassley is still delayed. He will be here. We do plan on hearing from Senator Grassley today. He has just asked for our indulgence. And we'll certainly accommodate the Senator.

We will call our next panel. Dr. Paul Herbert Chew, President of U.S. Research and Development Division at Sanofi-aventis Pharmaceuticals; Dr. Fred Eshelman, Chief Executive Officer at PPD; and Ms. Sharon Hill Price, Chief Executive Officer and Chairman of the Board at the Copernicus Group IRB. It is the policy of this Subcommittee to take all testimony under oath. Please be advised you have the right within the Rules of the House to be advised by counsel during your testimony. Do any of our witnesses wish to be represented by counsel? Dr. Chew, would you please state the name of your counsel.

Dr. CHEW. Mr. Chairman, the counsel for the company is Mr. Daniel Kracov from Arnold and Porter.

Mr. STUPAK. OK. Dr. Eshelman.

Mr. ESHELMAN. Counsel is present. Mr. Robert Nicholas from McDermott Will.

Mr. STUPAK. And Ms. Price.

Ms. PRICE. My counsel are Ann Begley and Gary Yingling from K&L Gates here in D.C.

Mr. STUPAK. OK. I'm going to ask you to please rise, raise your right hand and take the oath.

[Witnesses sworn.]

Mr. STUPAK. Please let the record reflect that all witnesses replied in the affirmative. Each and every one of you are under oath. We will take an opening statement for 5 minutes. You may submit a longer statement for the record if you wish.

Mr. STUPAK. From our left, we'll start with you Dr. Chew. If you would start please, sir, for an opening statement.

**STATEMENT OF DR. PAUL HERBERT CHEW, PRESIDENT, U.S.
RESEARCH AND DEVELOPMENT DIVISION, SANOFI-AVENTIS
PHARMACEUTICALS**

Dr. CHEW. Thank you. Chairman Stupak, Congressman Walden and Members of the Subcommittee, I'm Dr. Paul Chew, President of Research and Development for Sanofi-aventis U.S. Sanofi-aventis is a global research-based company dedicated to improving human health and addressing unmet medical needs. Patient safety is our highest priority. I'm here today to provide the Sanofi-aventis perspective on the issues raised regarding our antibiotic Ketek, and in particular, the conduct of Study 3014. I'll focus first on the issues that arose in Study 3014 and then on what we learned from this experience. While I was not directly involved in the design or conduct of Study 3014, I've carefully reviewed the matter. Let me begin by stating that we fully acknowledge that Aventis made several incorrect assumptions about achieving compliance in Study 3014.

We greatly regret that Dr. Kirkman-Campbell's fraud and certain problems at other sites were not identified or confirmed during the study. And we respect FDA's actions regarding Study 3014. We strongly believe however, that Aventis submitted the Study 3014 report in good faith believing that the good clinical practice issues that had been addressed—that had been addressed under the preestablished monitoring plan and that the integrity of the safety data had not been effected. Study 3014 was the first large preapproval anti-infective drug study conducted in a usual care setting.

The purpose of this supplemental study, which was conducted after the completion of the pivotal studies for the drug, was to further assess adverse events of special interest seen in the earlier pivotal studies, but in the real world physician's office setting and patient population. Study 3014 was never intended to find every possible adverse effect event that could occur in the future Ketek population. No single study can accomplish that goal. In conducting the study Aventis at its contract clinical research organization, PPD identified and addressed a range of deviations from good clinical practice. At the highest enrolling site, that of Dr. Kirkman-Campbell, numerous GCP violations were identified during the trial and questions were raised at that time regarding the legitimacy of certain practices and data.

Those questions were actively investigated by Aventis and PPD under a documented investigation plan. And Aventis and PPD required Dr. Kirkman-Campbell to act upon their findings. As you know, however, FDA subsequently documented investigative fraud at that site and Dr. Kirkman-Campbell pled guilty to falsifying clinical records. Aventis cooperated fully in that initial investigation and Sanofi-aventis has cooperated fully on all subsequent investigations. While numerous GCP violations were identified, it's our belief that Aventis was unable to confirm actual fraud at the Kirkman-Campbell site. It's important to know that FDA criminal investigators have tools at their disposal that are typically unavailable to study sponsors and monitors. So what have we done to address what we know now about Study 3014?

Since 2004, when Sanofi acquired Aventis to sponsor the Study, we've undertaken a comprehensive review of our policies, procedures and training. Let me share a few of these lessons learned. First, it's important to improve our ability to address investigator fraud. Sanofi-aventis has enhanced its approach to investigating potential fraud and persistent GCP noncompliance. We have also mandated additional training in these areas for all personnel engaged in study activities. This experience has also reinforced the importance of transparency in our interactions with FDA. In retrospect, Aventis could have been more proactive in bringing the issues encountered at high enrolling sites, and particularly the Kirkman-Campbell site, to the attention of the agency.

In addition, more real-time on-site monitoring may have mitigated many of the issues in Study 3014. Thus we've revised our approach to site initiation and monitoring to ensure that study sites are visited shortly after the first subjects are enrolled to help ensure protocol adherence and to detect potential problems. Sanofi-aventis has also implemented systems and procedures to strengthen the evaluation, the selection and training of investigators.

Finally, many of the problems in Study 3014 occurred at high enrolling sites. We recognize that strict controls of site enrollment are essential in every study. Our current procedures incorporate new provisions limiting the number of patients enrolled and the rate of enrollment.

In closing Mr. Chairman, we recognize the serious nature of the problems identified in Study 3014. However, I urge you to separate out what we know now about Dr. Kirkman-Campbell and other sites from what Aventis was able to determine at the time as the study sponsor. We have provided FDA with detailed information on the comprehensive steps that we've taken. The FDA, Congress and the American public have the unequivocal commitment to Sanofi-aventis to rigorous and compliant clinical research.

On behalf of Sanofi-aventis, thank you for the opportunity to participate in today's hearing. We understand your interest in these important issues and I look forward to answering your questions. I ask that my statement be included in the record of today's hearing. Thank you.

[The prepared statement of Dr. Chew, M.D. follows:]

Summary:

**Statement of
Paul Herbert Chew, M.D.
President, Research and Development
sanofi-aventis U.S. Inc.**

February 12, 2008

- The safety and efficacy of Ketek® (telithromycin), an innovative antibiotic now indicated in the U.S. for treatment of community-acquired pneumonia, are well-supported by clinical data. In 2006, after a comprehensive review, FDA and two advisory committees concluded that Ketek® continues to have a favorable benefit-risk profile..
- Study 3014, conducted by Aventis in Winter 2001-2002, was the first large, pre-approval "usual care" study for an anti-infective drug. The study involved over 1,800 investigators treating over 24,000 patients in a brief time period. It is important to note that this "real world" study supplemented the typical pivotal clinical trials, and was never designed to find every possible adverse event that could occur in the future Ketek® patient population.
- Extensive records confirm that Aventis and the study monitor PPD sought to address investigator Good Clinical Practice (GCP) deviations. At the highest enrolling site, that of Dr. Kirkman-Campbell, numerous GCP deviations were identified and questions were raised regarding the legitimacy of certain practices and data. Those questions were actively investigated by Aventis and PPD under a documented investigation plan, which required the investigator to act upon their findings.
- Despite those efforts, criminal fraud was subsequently discovered by FDA at that site. Dr. Kirkman-Campbell, an independent physician investigator, pled guilty to falsifying clinical trial records. Aventis cooperated fully in the investigation of Dr. Kirkman-Campbell -- as sanofi-aventis has cooperated in all of the extensive investigations into Study 3014. It is important to note that FDA criminal investigators have tools at their disposal, such as interviewing patients and various investigative techniques, that are typically unavailable to study sponsors and monitors. We must separate out what we know now about Dr. Kirkman-Campbell and other sites from what Aventis was able to determine at the time as the study sponsor.
- We greatly regret that Dr. Kirkman-Campbell's fraud was not confirmed during the study, as well as the study compliance problems later identified at other sites based upon additional information obtained through extensive post-study reviews. We firmly believe, however, that Aventis submitted the study report in good faith, believing that the GCP issues at the various sites had been addressed within the context of the monitoring plan and did not affect the safety data that was the focus of the study. We fully respect FDA's decision not to rely upon Study 3014 to support the approval of Ketek®. FDA's review -- including its ultimate decision to approve Ketek -- was quite rigorous and appropriate.
- We have learned important lessons from Aventis' Study 3014 experience. In addition to changes in policies, practices and personnel since Sanofi acquired Aventis in 2004, we have undertaken a comprehensive review of the lessons learned from Study 3014 to ensure that sanofi-aventis' policies, procedures, and training reflect those lessons. The changes we have instituted have been presented to FDA, and are detailed in my testimony.
- We recognize that the problems identified in Study 3014 are a very serious matter. FDA, Congress and the American public have the unequivocal commitment of sanofi-aventis to rigorous and compliant clinical research.



**Statement
of
Paul Herbert Chew, M.D.
President
Research and Development
sanofi-aventis U.S. Inc.**

**Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives**

February 12, 2008

Chairman Stupak, Ranking Member Shimkus, and Members of the Subcommittee, I am Dr. Paul Chew, President, Research and Development, for sanofi-aventis U.S. Inc.

I am here today to provide you with my perspective on the issues that have been raised regarding the development and approval of our antibiotic Ketek® and, in particular, the conduct of the clinical trial Study 3014. I also hope to contribute to your consideration of the broader pharmaceutical research and safety issues on the Subcommittee's agenda.

I would first like to provide some background about sanofi-aventis. We are an innovative, research-based company dedicated to improving health by discovering and developing new medicines that address unmet medical needs and ease or eliminate the burdens of illness and disease. Our research and development budget is one of the highest in the

industry, and we have research facilities around the world, including four U.S. R&D centers that employ approximately 2,600 scientists, physicians and support staff.

Patient safety is our highest priority at sanofi-aventis, and we are committed to conducting rigorous clinical research designed to provide a comprehensive understanding of the safety and efficacy of our products. Through ongoing monitoring and analysis of reported adverse events and other data, we thoroughly evaluate new information relating to our medicines. We are committed to timely and transparent communication with regulatory agencies around the world to ensure that benefit and risk information is clearly and accurately reflected in labeling.

Three key questions that I would like to address today are:

- One, what is the value of Ketek® and should the drug be on the market today?
- Two, what are the basic facts relating to Study 3014, and what went wrong in the study?
- And three, what have we learned from this experience?

The Value of Ketek® (telithromycin)

First, what is the value of Ketek® and should it be on the market today?

From a public health perspective, the development of new antibiotics is imperative. Antibiotic resistance is considered one of the world's most pressing infectious disease

challenges. Many significant bacterial infections are becoming resistant to commonly prescribed treatments, and such treatment-resistant pathogens can often require intensive interventions, including extensive hospital stays. The total cost of antimicrobial resistance in the U.S. was estimated by the Institute of Medicine to be nearly \$5 billion annually. For several reasons, few pharmaceutical companies have pursued development of this important class of products. These factors include the costs of product development, the inherent scientific difficulties of antibiotic research, evolving standards for evaluation of safety and efficacy, and resistance concerns.

Despite these challenges, Aventis pursued the development of Ketek® as the first in a new class of antibiotics called ketolides. Ketek® has a unique mechanism of action, targeting two binding sites on common respiratory pathogens, including multi-drug resistant versions of the important pathogen *S. pneumoniae*.

Ketek® or telithromycin, now indicated in the U.S. for treatment of a very serious condition called 'community-acquired pneumonia, is well-supported by clinical data. Aventis' new drug application included 14 controlled phase III clinical trials, two additional studies, and extensive data from experience in more than 4 million patients taking Ketek® in other countries.

We recognize that issues have been raised regarding the use of non-inferiority study designs in the development of antibiotic products, including Ketek®. Such studies involve demonstrating non-inferiority of the new drug to an existing, FDA-approved comparator antibiotic drug. There has been a legitimate scientific debate regarding the use of non-inferiority studies to support efficacy for certain antibiotic indications, and it is

important to understand that such questions have been considered by FDA only relatively recently. In fact, in late 2006 FDA formulated its current position that non-inferiority studies would not be accepted to support the approval of indications for acute bacterial sinusitis (ABS) or acute exacerbation of chronic bronchitis (AECB), a position the Agency reiterated at the Advisory Committee meeting held in December 2006 to consider the appropriate indications for Ketek.

The use of non-inferiority studies to support the approval of Ketek® was consistent with the standards for antibiotic development then in place. The protocols for the Ketek® pivotal studies were agreed upon with FDA, and were considered the most appropriate and ethical approach to demonstrating efficacy for the indications under study. Thus, the issues that have been raised regarding non-inferiority trials are not Ketek®-specific. Indeed, virtually all of the currently marketed antibiotic products for these indications were approved based upon such study designs. In fact, we believe the database supporting Ketek® is one of the largest bodies of information available for any antibiotic at the time of initial approval.

As you are well aware, a supplemental "usual care" study – Study 3014 – was also conducted. However, the FDA has indicated that it did not rely upon Study 3014 to approve Ketek.®

The data on Ketek® has undergone intensive review. Most recently, in December of 2006, the FDA and two of its expert advisory committees concluded that Ketek® continues to have a positive benefit-risk profile for community-acquired pneumonia. The recently updated labeling for the product reflects a careful balancing of benefits and risks.

This is not uncommon in this therapeutic area; a number of common antibiotics are associated with serious warnings and contraindications. So, to the extent there is a question whether Ketek®, an innovative antibiotic, should have been approved in the first place, and whether it should remain on the market, the answer is yes.

Study 3014

Next, let me address the basic facts of Study 3014, and what went wrong in that study. Although I was not directly involved in the design or conduct of Study 3014, I have had an opportunity to review the matter carefully.

The Ketek® new drug application (NDA) was submitted to the FDA on February 28, 2000, and the Agency convened a meeting of the Anti-Infective Drugs Advisory Committee on April 26, 2001 to discuss the data and seek expert input regarding the overall benefit-risk profile. After consideration of extensive data from 14 pivotal clinical trials and two additional safety studies, the Advisory Committee believed that certain potential safety signals seen in those trials – the controlled clinical trials typically done to support drug approval – should be further explored in a supplemental large safety study. As the Advisory Committee recommended, FDA asked for such a study to provide further evaluation of infrequent hepatic, visual, cardiac, and vasculitic “adverse events of special interest,” or “AESIs.”

This study, known as Study 3014, was conducted by Aventis in the Winter of 2001-2002, and it was the first large “usual care” study conducted pre-approval for an anti-infective drug. This type of study involves trying to study an unapproved drug in a large

population of patients at many study sites in order to evaluate safety in the typical physician's office or "real world" setting involving treatment of a more diverse range of patients.

It is important to note that the study was never designed to find every possible adverse event that could occur in the future Ketek® patient population. No single study can accomplish that goal. Rather, as agreed upon with FDA, Study 3014 was focused on further characterizing -- in the usual care setting -- the "adverse events of special interest" that had already been identified in the controlled clinical trials.

Study 3014 was unusually large and complex, involving the coordination of over 1,800 investigators treating over 24,000 patients in a brief time period. Aventis consulted with FDA about the study design, submitted the draft monitoring plan, and hired experienced contractors to implement training and provide monitoring in an effort to ensure investigator compliance.

At the time of the study, Aventis believed that the compliance monitoring efforts were appropriate to the task at hand. For example:

- Approximately 93,000 weekly and other monitoring calls were made to investigator sites.
- Over 99% of the sites that enrolled 16 or more patients, and 100% of sites where the physician had not previously served as a study investigator and which enrolled 5 or more patients, received an on-site monitoring visit.

- Approximately 38% of enrolled subjects had complete source verification of study data by PPD.
- As the focal point of the study, AESIs were tracked and rigorously assessed by outside experts.

During the study, Aventis and its contract research organization PPD identified numerous deviations from good clinical practices, or "GCPs", at various investigator sites. GCP deviations occur in virtually every large clinical study. Such issues, which include protocol deviations, failure to initial or sign documents, or other incomplete documentation, are typically successfully addressed through corrective actions. Thus, FDA's regulations call upon companies sponsoring studies to first secure compliance with applicable requirements and, if such compliance cannot be secured, to end the investigator's participation in the study. Extensive records confirm that Aventis and PPD sought to correct or address GCP deviations, consistent with FDA regulations.

At the highest enrolling site, that of Dr. Kirkman-Campbell, numerous GCP deviations were identified and questions were raised regarding the legitimacy of certain practices and data. Contrary to the allegations that have been made, those questions were actively investigated by Aventis and PPD under a documented investigation plan, and Aventis and PPD required Dr. Kirkman-Campbell to act upon their findings.

But, as you know, criminal fraud was subsequently discovered by FDA at that site, and Dr. Kirkman-Campbell, an independent physician investigator, was criminally prosecuted for her actions and pled guilty to falsifying clinical trial records. Aventis cooperated fully in the investigation of Dr. Kirkman-Campbell -- as we have cooperated in all of the

extensive investigations into Aventis' conduct in Study 3014 -- providing access to employees and thousands of pages of documents. At FDA's request, the company also submitted independent reviews of certain study sites, and a reanalysis of the study without the Kirkman-Campbell data. Notably, the exclusion of the Kirkman-Campbell data in this reanalysis did not impact the safety profile observed in the trial.

Although the investigator fraud at the site is now in clear focus, based upon our review, we believe Aventis was unable to confirm at the time that fraud had occurred at the Kirkman-Campbell site, as opposed to good clinical practice deviations. In evaluating Aventis' conduct as sponsor of Study 3014, it is important to note that FDA criminal investigators have tools at their disposal, such as interviewing patients and various investigative techniques, that are typically unavailable to study sponsors and monitors. We must separate out what we know now about Dr. Kirkman-Campbell and other sites from what Aventis was able to determine at the time as the study sponsor.

I can tell you that we greatly regret that Dr. Kirkman-Campbell's fraud was not confirmed during the study, as well as the problems later identified at other sites. With the benefit of hindsight and additional information obtained through extensive post-study review and subsequent information made available from FDA's inspections, sanofi-aventis acknowledges that Aventis was unable to secure compliance with the investigational plan and applicable FDA regulations at a number of sites. However, we firmly believe that Aventis submitted the study report in good faith, believing that the GCP issues at the various sites had been addressed and did not affect the safety data which was the focus of the study.

In this regard, it is worth noting the conclusions stated by Dr. Joanne Rhoads, the Director of FDA's Division of Scientific Investigations at the time Study 3014 was investigated, at the comprehensive December 2006 Advisory Committee meeting on Ketek®. At that meeting, Dr. Rhoads stated:

These are difficult studies to do and to monitor and inspect....Monitoring is highly variable. In my experience, even when fraud exists, monitors often don't find it. Even when serious problems exist, monitors often don't find it....And there were problems definitely identified. But, considering the nature of the trial and the extent of the problem, we did not see direct evidence that this information was ignored by the company.

Although we agree with Dr. Rhoads' observations, we are determined to learn from this experience.

Ultimately, FDA decided not to rely upon Study 3014 to support the approval of Ketek® in April 2004. We fully respect that decision. However, Ketek® was approved on the basis of a large body of controlled clinical trials involving over 4,300 Ketek®-treated subjects, post-marketing data from millions of patients outside the United States, and other data provided to the Agency. Specifically, Aventis submitted extensive post-marketing safety data from use in actual physician practice in other countries, including countries of the European Union, where approximately 4 million patients had been treated with the drug. Such extensive data were not available when Study 3014 was requested by FDA in 2001. Overall, we believe FDA's review was quite rigorous and appropriate.

Lessons Learned

Finally, in addition to changes in policies, practices and personnel since Sanofi acquired Aventis in 2004, we have also undertaken a comprehensive review of the lessons learned from Study 3014 to ensure that sanofi-aventis' procedures -- and associated training -- reflect those lessons. Let me share with you a few of the steps we have taken.

First, in addition to reliance upon the integrity of physician investigators, we in the industry must improve our ability to detect investigator fraud in clinical studies. At sanofi-aventis, we have enhanced our approach to investigating potential fraud, and mandated additional training in these areas for all personnel engaged in study management, monitoring and auditing activities. We have also focused on improving our procedures for addressing persistent investigator non-compliance.

We also recognize that we must be more transparent in our interactions with the FDA. In retrospect, Aventis could have been more proactive in bringing the issues encountered at high-enrolling sites, and particularly the highest enrolling site, to the attention of the Agency so it could have used its superior knowledge and investigative tools to evaluate the potential for fraud at an earlier point. We have revised our procedures to address this lesson. However, additional guidance on reporting situations in which the sponsor has serious investigator compliance concerns -- but not confirmation of fraud -- would benefit our industry as a whole.

We also think that industry would benefit from additional guidance on addressing the more general compliance challenges in these very large, usual care study designs, particularly as requests for such studies become more frequent. In retrospect, more real-

time on-site monitoring may have mitigated many of the issues in Study 3014. We have revised our site initiation and initial monitoring approach to ensure that clinical study sites are visited, on site, shortly after the first subject has been enrolled, in order to assure protocol adherence and detect potential problems.

Sanofi-aventis has also implemented systems and procedures to strengthen the evaluation, selection and training of investigators. A comprehensive plan to validate each investigator's qualifications and capabilities prior to enrollment is essential in every study. Although Aventis and its contractors undertook significant efforts to train the investigators in Study 3014, in retrospect more intensive training of investigators may have resulted in a better compliance outcome.

Finally, many of the problems in Study 3014 occurred at the high-enrolling sites. At the time, although the study protocol included a recommendation as to enrollment numbers, Aventis believed that higher levels of enrollment were feasible in the usual care setting. In retrospect, we recognize that strict limits on enrollment are essential in every study, and we have instituted procedures to further limit both the number of patients enrolled and the rate of enrollment.

These are just a few of the lessons we have learned from this difficult experience.

In closing, we recognize that the problems identified in Study 3014 are a very serious matter. As you know, FDA recently issued an extensive Warning Letter documenting the findings from its investigation of Aventis' handling of Study 3014. We have responded with detailed information on the comprehensive steps that sanofi-aventis has taken, and

will continue to take, to address the lessons we have learned. As a company that places the highest priority on patient safety, the FDA, Congress and the American public have the unequivocal commitment of sanofi-aventis to rigorous and compliant clinical research.

Mr. Chairman, Ranking Member Shimkus, and Members of the Subcommittee, on behalf of sanofi-aventis U.S., thank you for the opportunity to participate in today's hearing. We understand your interest in these important issues, and we look forward to answering your questions. I ask that my statement be included in the record of the today's hearing.

Mr. STUPAK. Your statement is included in the record, as all statements are. Dr. Eshelman, do you have an opening statement please, sir?

**STATEMENT OF DR. FRED ESHELMAN, CHIEF EXECUTIVE
OFFICER, PPD, INC.**

Mr. ESHELMAN. Yes, sir, I do have a statement. Good morning, Chairman Stupak, Congressman Walden and members of the subcommittee. I'm Fred Eshelman, founder and CEO of Pharmaceutical Product Development, also known as PPD. It is my pleasure to be here today as a representative of PPD. At this time, I also ask that my written statement be made part of the record. PPD is a global contract research organization or CRO. We provide drug development services to pharmaceutical, biotechnology and medical device companies and also government organizations, all of which are referred to as sponsors. As a CRO, PPD is hired by sponsors of clinical trials to perform obligations of the sponsors arising under the Federal Food Drug and Cosmetic Act and FDA's clinical study related regulations. Principally, 21 C.F.R. Parts 50, 56, 312 and 812. Under FDA regulations a sponsor may transfer the legal obligations for compliance with regulatory requirements to a CRO. FDA regulations require that any delegation of authority be set forth in a written agreement.

Under FDA regulations any obligation that is not specifically transferred to the CRO is retained by the sponsor. These requirements are set forth in 21 C.F.R. Section 312.52. In the fall of 2001, PPD contracted with Aventis to perform specific services in connection with the study of Ketek Study 3014. These obligations are set forth in detail in my written testimony. Other than these enumerated obligations Aventis did not contract with PPD to perform additional services. With regard to addressing investigative misconduct Federal regulations require that the sponsor either secure compliance or end the investigator's participation in the study. If an investigator is terminated then the FDA must be notified. This requirement is set forth in 21 C.F.R. Section 312.56(b).

Under our contract with Aventis, PPD was to report any investigator that did not comply with the study plan to Aventis. We did not, however, have the authority to end an investigator's participation in the study or to report an investigator's conduct to the FDA.

During Study 3014, PPD staff uncovered compliance concerns at the site of an investigator now familiar to this subcommittee, Dr. Anne Kirkman-Campbell. PPD's monitoring team made its first visit to the Kirkman-Campbell site in late November of 2001. In February of 2002 PPD's monitoring team visited the Kirkman-Campbell site for a second time. During the visit, PPD personnel determined that the site failed to document critical source information.

PPD staff also found many inconsistencies and modifications regarding patient signatures on informed consent forms. Further, subjects appeared to have been randomized to the study in extremely high volumes during short time intervals. Additionally, PPD monitors found staff at the Kirkman-Campbell site to be uncooperative.

At the same time with the February visit, PPD also analyzed data from the Kirkman-Campbell site regarding patient blood samples due to concerns raised by our staff. Based upon PPD's review, there appeared to be a lack of variability among blood samples shared by many patients. The data suggested that the Kirkman-Campbell site engaged in blood sample splitting, which is assigning a patient's blood sample to one or more patients in order to maximize enrollment totals. In light of these concerns, PPD staff asked for a conference call with Aventis.

On the March 4, 2002 call, PPD personnel set forth in detail their concerns about the Kirkman-Campbell site. At the conclusion of that call, Aventis said that it would look into Kirkman-Campbell's compliance issues and devised an action plan. First, Aventis said that it would initiate its own analysis of the Kirkman-Campbell lab data to determine the probability that the site had engaged in blood sample splitting. Ultimately, Aventis informed PPD that it had analyzed the lab data and that the data was not indicative of scientific misconduct. Second, the Aventis study manager was tasked with contacting Dr. Kirkman-Campbell about the site's informed consent and randomization problems raised by PPD. Ultimately, Aventis and PPD sent a follow-up letter to Dr. Kirkman-Campbell raising these issues. Mr. Chairman, on behalf of PPD, I would like to thank you for the opportunity to testify before this subcommittee. I hope that my testimony provides the subcommittee with a better understanding of PPD, the regulatory and contractual framework that governs our conduct and our role in the Kirkman-Campbell matter. I would welcome any questions that you have. Thank you.

[The prepared statement of Mr. Eshelman follows:]

**STATEMENT OF
FRED N. ESHELMAN, Pharm.D
CEO, PHARMACEUTICAL PRODUCT DEVELOPMENT, INC.
FOR
THE HOUSE ENERGY AND COMMERCE
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
FEBRUARY 12, 2008**

Introduction

Good morning Chairman Stupak, Congressman Shimkus, and Members of the Subcommittee. I am Fred N. Eshelman - the founder of Pharmaceutical Product Development, Inc. ("PPD"). Since July 1990, I have served as its Chief Executive Officer. It is my pleasure to be here today as a representative of PPD. Attached to this statement is a copy of my *curriculum vitae*.

PPD

PPD is a global Contract Research Organization ("CRO"). We provide drug development services to pharmaceutical, biotechnology, and medical device companies and government organizations – all of which are referred to as sponsors.

As a CRO, PPD is hired by sponsors of clinical trials to perform obligations of the sponsors arising under the Federal Food, Drug and Cosmetic Act and FDA's clinical study related regulations, principally 21 CFR Parts 50, 56 and 312 and/or 812. Under FDA regulations, a sponsor may transfer the legal obligation for compliance with regulatory requirements to a CRO.

Sponsors may contract with CROs to perform a wide variety of tasks. Often, a CRO is asked to monitor a study's investigation sites in order to confirm that a site's conduct is consistent with the protocol, applicable regulations, and Good Clinical Practices ("GCPs"). In

addition, a CRO may also be asked to take part in the selection and training of investigators, provide data management services, perform biostatistical analysis of study data, conduct quality assurance, prepare / submit regulatory filings, or provide medical writing services in support of a new drug application or final study report. In some cases, a sponsor may simply delegate full responsibility for the administration of a study to a CRO.

Regardless of the scope of the delegation, the FDA regulations require that any delegation of authority be set forth in a written agreement. Under FDA regulations, any obligation that is not specifically transferred to the CRO is *retained* by the sponsor. These requirements are set forth in 21 CFR section 312.52.

Ketek (Study 3014)

In the Fall of 2001, PPD contracted with Aventis to perform specified services in connection with the study of Ketek (Study 3014). Study 3014 was designed by Aventis as a large clinical trial and involved 24,000 patients and 1,800 investigative sites across the United States. Under the terms of our agreement, the following tasks were delegated to PPD:

1. Recruit and select physicians to serve as site investigators, negotiate site agreements, and make site payments;
2. Assist a third-party vendor in training investigators on study policies and procedures;
3. Create an Interactive Voice Response System to randomize patients and manage the supply of the study drug to sites;
4. Monitor study sites;

5. Track site documentation and communications;
6. Facilitate the transfer of case report forms submitted from the sites to Aventis's data management vendor and assist in resolving queries; and
7. Notify Aventis of serious adverse events and adverse events of special interest among patients.

Other than these obligations, Aventis did not contract with PPD to perform additional services. For instance, PPD did not provide any data management, medical writing, quality assurance, or biostatistics services.

With regard to addressing investigator misconduct, federal regulations require that the sponsor either secure compliance or end the investigator's participation in the study. If an investigator is terminated, then the FDA must be notified. This requirement is set forth in 21 CFR section 312.56(b). Under our contract with Aventis, PPD was to report any investigator that did not comply with the study plan to Aventis. We did *not*, however, have the authority to end an investigator's participation in the study or to report an investigator's conduct to the FDA.

Kirkman-Campbell Site

During the course of its monitoring activities in Study 3014, PPD's staff uncovered compliance concerns at the site of an investigator now familiar to this Subcommittee, Dr. Anne Kirkman-Campbell. In October 2001, Dr. Kirkman-Campbell was engaged as an investigator for Study 3014. She managed a medical practice in Gadsden, Alabama. As this Subcommittee knows, Dr. Kirkman-Campbell ultimately enrolled 407 patients over a 3 month span, which established her site as Study 3014's highest enroller.

PPD's monitoring team made its first visit to the Kirkman-Campbell site in late November 2001. In February 2002, PPD's monitoring team visited the Kirkman-Campbell team for a second time. During the visit, PPD personnel determined that the site failed to document critical source information. PPD staff also found many inconsistencies and modifications regarding patient signatures on Informed Consent forms. Further, subjects appeared to have been randomized for the study in extremely high volumes during short time intervals. In some circumstances, 20 or more patients were randomized approximately 1 minute apart from each other. Additionally, PPD monitors found staff at the Kirkman-Campbell site uncooperative.

At the same time of the February visit, PPD also analyzed data from the Kirkman-Campbell site regarding patient blood samples due to concerns raised by our staff. Based upon PPD's review, there appeared to be a lack of variability among blood samples shared by many patients. The data suggested that the Kirkman-Campbell site engaged in "blood sample-splitting," which is assigning a patient's blood sample to one or more patients in order to maximize enrollment totals.

March 4, 2002 Conference Call

In light of these concerns, PPD staff asked for a conference call with Aventis. We were concerned about the information we had acquired and wanted to ensure that we brought this information to Aventis's attention. During a March 4, 2002, conference call with employees at Aventis, PPD personnel set forth in detail their concerns about the Kirkman-Campbell site.

At the conclusion of that call, Aventis said that it would look into Kirkman-Campbell's compliance issues and devised an action plan. First, Aventis said it would initiate its own analysis of the Kirkman-Campbell lab data to determine the probability that the site had engaged

in blood sample-splitting. Ultimately, Aventis informed PPD that it had analyzed the lab data and that the data was not indicative of scientific misconduct. Second, the Aventis study manager was tasked with contacting Dr. Kirkman-Campbell about the site's informed consent and randomization problems raised by PPD. Ultimately, Aventis and PPD sent a follow-up letter to Dr. Kirkman-Campbell, raising these issues. Aventis did not ask PPD to terminate Dr. Kirkman-Campbell as an investigator or to report her conduct to the FDA.

Conclusion

Mr. Chairman, on behalf of PPD, I would like to thank you for the opportunity to testify before this Subcommittee. I hope that my testimony provides the Subcommittee with a better understanding of PPD, the regulatory and contractual framework that governs our conduct, and our role in the Kirkman-Campbell matter. I welcome any questions that you have.

CHIEF EXECUTIVE OFFICER

Fred N. Eshelman

EXPERIENCE

PPD, INC., WILMINGTON, NC (PPDI, NASDAQ)

Chief Executive Officer and Vice Chairman

July 1990 - Present

GLAXO INCORPORATED, RESEARCH TRIANGLE PARK, NC

Senior Vice-President, Development Division

January 1989- June 1990

Responsible for Metabolism, Toxicology and Project Planning, Pharmaceutical Development, Regulatory Affairs, Biostatistics/Data Management, and Phase III Clinical. Co-Chairman, US-UK Joint Development Committee, Member of Executive Committee and Board of Directors, Glaxo Inc. and Glaxo International Research Limited.

Vice-President, Clinical Operations

September 1988 - December 1988

Responsible for all Glaxo Inc. clinical research (Phases I-V) and Biostatistics/Data Management. Member of Operations Committee.

PHARMACEUTICAL PRODUCT DEVELOPMENT, WILMINGTON, NC

President and Founder

June 1985 - August 1988

Clinical research management company involved in all phases of product development in a variety of therapeutic areas.

BOEHRINGER-MANNHEIM CORPORATION, ROCKVILLE, MD

Director of Clinical Research

October 1984 - June 1985

GLAXO INCORPORATED, RESEARCH TRIANGLE PARK, NC

Group Director, Clinical Research
May 1983 - September 1984

Associate Director, Clinical Research
August 1979 - April 1983

BEECHAM LABORATORIES, BRISTOL, TN

Associate Director, Clinical Research
December 1977 - August 1979

Director of Professional Relations
August 1977 - May 1978

BIO/BASICS INTERNATIONAL, NEW YORK CITY, NY

Assistant Director, Clinical Operations
1976 - 1977

EDUCATION

- Harvard Business School
OPM Class 22
1993 - 1995
- University of Cincinnati, Division of Graduate Studies
Doctor of Pharmacy
1974
- Cincinnati General Hospital, Rotation to Cincinnati V.A. Hospital
Clinical Pharmacy Residency
1972 - 1974
- Duke University, Durham, NC
Academic portion, Physicians' Associate Program
1971 - 1972
- University of North Carolina, Chapel Hill, NC
Bachelor of Science (Pharmacy)
1972

- High Point University, High Point, NC
Chemistry
1966 - 1969

ACADEMIC EXPERIENCE

UNIVERSITY OF NORTH CAROLINA, SCHOOL OF PHARMACY, CHAPEL HILL, NC

Adjunct Professor & Board of Visitors
Present

UNIVERSITY OF ILLINOIS MEDICAL CENTER, COLLEGE OF PHARMACY

Clinical Assistant Professor
1974 - 1976

PUBLICATIONS

Available upon request.

Mr. STUPAK. Ms. Price, for your opening statement, please.

STATEMENT OF SHARON HILL PRICE, CHIEF EXECUTIVE OFFICER AND CHAIRMAN OF THE BOARD OF DIRECTORS, COPERNICUS GROUP IRB.

Ms. PRICE. Thank you.

Mr. STUPAK. Press that button there.

Ms. PRICE. I found it now. OK.

Mr. STUPAK. Thanks.

Ms. PRICE. Good morning. My name is Sharon Hill Price, and I am the chief executive officer of Copernicus Group Institutional Review Board. I would like to thank the committee for providing me an opportunity to make a statement today.

An IRB's regulatory mandate is to assure the protection of the rights and welfare of human subjects in clinical trials. In our current system, the IRB's responsibility to protect subjects is shared with the investigators, the institutional sponsor, and the government. An IRB carries out its unique role by reviewing study information provided by sponsors and investigators and determining whether the research adheres to the ethical principles of the Belmont Report and Federal regulations. As CEO, my responsibilities are to direct the administrative functions at Copernicus, while the separate ethical review function is conducted and controlled by our independent Institutional Review Board.

On a personal note, I built this company from the ground up, and have always strived to assure that Copernicus provides the highest quality ethical review. We are deeply troubled with what has happened in 3014, and I, along with the dedicated employees at my site, certainly are interested in the findings of this committee.

In August 2001, Copernicus was contacted by PPD and asked to serve as IRB of record for Study 3014, a clinical trial sponsored by Aventis. This was a large, multicenter trial, as you know, conducted over a relatively short duration of approximately 6 months.

Copernicus initially reviewed and approved the protocol as well as the consent document that was to be used by each investigator as they worked in the process with their subjects. Additionally, the IRB reviewed information for each of the investigators selected by the sponsor and provided oversight for any information that was provided by the investigator throughout the study.

One of those investigators was Dr. Kirkman-Campbell. Dr. Kirkman-Campbell's submission packet was reviewed around October 2001, and she was granted IRB approval to serve as a Study 3014 investigator.

At a committee hearing last year, Ann Marie Cisneros, a former PPD employee, testified that during a monitoring visit to the Kirkman-Campbell site in February of 2002, she had called Copernicus and spoken to the President and informed her of concerns found at the site. Her statement surprised us at Copernicus, because no one on the staff at that time was aware of any such call having been made. And I, as President, did not recall any such call. Furthermore, at the time, our searches of documents did not turn up any evidence of a call from Ms. Cisneros.

However, on the afternoon of Wednesday, January 23rd, 2008, in preparation for a meeting with the committee staff, Copernicus did

find documentation of an anonymous call being taken by one of our professionals on February 24th, 2002—excuse me, February 21st, 2002. Based upon its content, this memo appears to describe a call from Ms. Cisneros, and it was, I think, briefly mentioned earlier this morning. For some reason, and contrary to both procedure and training, this memo was not forwarded to a supervisor by the employee or to the Institutional Review Board, as it should have been at the time. Neither was the document placed in the investigator file as it should have been.

We have intensely investigated this matter, but we simply do not have an answer for why this lapse occurred. Had the Board received the information, as it should have at the time, I am confident that the Board, the IRB, would have investigated the matter and taken appropriate action. While I cannot speak specifically to the independent decision the Board would have made, the action most likely would have included notifying the FDA about concerns of the investigator. This call should have been elevated to the Board. It was not. And on behalf of my company, I offer an apology for this deviation from our standard operating procedure.

In a recent interview in the *Journal of Clinical Research Best Practices*, Ms. Cisneros encouraged individuals to reach out to someone if they have concerns about research study conduct. I wholeheartedly agree with this advice. There are a number of options open to individuals faced with similar concerns, and the IRB should certainly be one of those options. The IRB is a place where both subjects and members of the research community can turn when issues about how a clinical trial is being conducted arise or if unanticipated problems that affect subject safety are suspected.

As additional regulatory guidance has been released over the years, Copernicus has continually reviewed and strengthened its policies and procedures in the past 6 years since Study 3014 ended. The IRB and professional support staff have been trained on existing policies, including those that govern the handling of unanticipated problems such as the kind that arose in Study 3014. Our ongoing process improvement efforts continue to strengthen our ability to recognize and appropriately address serious issues that rise to the level of unanticipated problems that pose risks to subjects or others.

Of additional significance, I think, to the committee is that Copernicus was one of the first groups to achieve a voluntary accreditation of our human subject protection program, this done by the Association for the Accreditation of Human Research Protection Programs, or AAHRPP, that is based right here in D.C. In order to attain this voluntary accreditation, Copernicus went through a rigorous self-assessment of our policies and practices and peer-review process to determine or to demonstrate that strict practice standards had met or exceeded the Federal human subject protection Requirements. Copernicus was recently reaccredited this past October.

In closing, I would like to say that Copernicus takes its role as a human subject protection entity very seriously, and has done so for the past 12 years since opening our doors in 1996. Although we sincerely apologize for the call that was not handled as it should have been 6 years ago, we remain proud of the important and inte-

gral role that IRBs plays in providing ethical review into clinical research.

Again, I appreciate the opportunity to testify today, although a little nervous, and I am prepared to answer any questions you might have. Thank you.

Mr. STUPAK. Thank you.

[The prepared statement of Ms. Price follows:]

STATEMENT OF SHARON HILL PRICE

Good morning. My name is Sharon Hill Price and I am the Chief Executive Officer of Copernicus Group Institutional Review Board. I would like to thank the Committee for providing me an opportunity to make a statement and testify today.

An IRB's regulatory mandate is to assure the protection of the rights and welfare of human subjects in clinical trials. In our current system, the IRB's responsibility to protect subjects is shared with the investigators, the institution or sponsor, and the government. An IRB carries out its unique role by reviewing study information provided by the sponsor and its agents, and by investigators engaged to perform the study, and determining whether the research adheres to the ethical principles outlined in the Belmont Report as set forth in federal regulations. As CEO, my responsibilities are to direct the administrative functions at Copernicus, while the separate ethical review function is conducted and controlled by our independent Institutional Review Board. On a personal note, I built this company from the ground up, and I take what happened in Study 3014 very seriously. I have always strived to assure that Copernicus provides high quality ethical review.

In August 2001, Copernicus was contacted by PPD and asked to serve as IRB of record for Study 3014, a clinical trial sponsored by Aventis Pharmaceutical, now known as the Sanofi-Aventis Group. This was a large, multi-center trial conducted over a relatively short duration of approximately 6 months. Copernicus initially reviewed and approved the protocol as well as the consent document that was to be used by investigators during the informed consent process with study subjects. Additionally, the IRB reviewed information for each of the investigators selected by the sponsor. One of those investigators was Dr. Kirkman-Campbell. Dr. Kirkman-Campbell's submission packet was reviewed and in October 2001 she was granted IRB approval to serve as a Study 3014 investigator.

At a committee hearing last year, Ann Marie Cisneros, a former PPD employee, testified that during a monitoring visit to the Kirkman-Campbell site in February 2002, she had called Copernicus and spoken to the President and informed her of concerns found at the site. Her statement surprised us at Copernicus because no one on our staff was aware of any such call having been received. Furthermore, at the time, our searches of documents did not turn up any evidence of a call from Ms. Cisneros.

However, on the afternoon of Wednesday, January 23, 2008, Copernicus found documentation of an anonymous call being taken by one of our professionals on February 21, 2002. Based upon its content, this memorandum appears to describe the call from Ms. Cisneros. For some reason, and contrary to both procedure and training, this memorandum was not forwarded to a supervisor or to the Institutional Review Board as it should have been at the time. Neither was the document placed in the investigator file as it should have been. We have intensively investigated this matter, but we simply do not have an answer as to why this lapse occurred. Had the Board received the information, as it should have, I am confident that the Board would have investigated the matter and taken the appropriate action. While I cannot speak to the independent decision that would have been made by the Board, this action most likely would have included notifying the FDA regarding concerns about the investigator. This call should have been elevated to the Board. On behalf of my company, I offer an apology for this deviation from our standard operating procedure.

In a recent interview in the Journal of Clinical Research Best Practices, Ms. Cisneros encouraged individuals to reach out to someone if they have concerns about research study conduct. I wholeheartedly agree with this advice. There are a number of options open to individuals faced with similar concerns and the IRB should certainly be one of those options. The IRB is a place where both subjects and members of the research community can turn when issues about how a clinical study is being conducted arise or if unanticipated problems that affect subject safety are suspected.

As additional regulatory guidance has been released, Copernicus has continually reviewed and strengthened its policies and procedures in the six years since Study 3014 has ended. The IRB and professional support staff have been trained on existing policies, including those that govern the handling of unanticipated problems such as the kind that arose in Study 3014 in 2002. Our ongoing process improvement efforts continue to strengthen our ability to recognize and appropriately address serious issues that rise to the level of unanticipated risk to subjects or others.

As part of that effort at strengthening our procedures, and of additional significance, Copernicus was one of the first groups to achieve accreditation of our human research protection program by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). In order to attain this voluntary accreditation, Copernicus went through a rigorous self-assessment and peer review process to demonstrate strict practice standards that meet or exceed federal human subject protection requirements. Copernicus was reaccredited this past October.

Copernicus has taken its role as a human subject protection entity seriously for the 12 years since first opening its doors in 1996. Although we sincerely apologize for the call that was not handled as it should have been six years ago, we remain proud of the important role that IRBs play in providing ethical review of clinical research. Again, I appreciate the opportunity to testify today and am prepared to answer any questions that you have.

Mr. STUPAK. Mr. Walden for questions, please.

Mr. WALDEN. I appreciate that, Mr. Chairman. Unfortunately, I have to leave for another meeting, so I appreciate your courtesy.

Ms. PRICE, this issue of the call sheet that appeared that you found—

Ms. PRICE. Yes.

Mr. WALDEN [continuing]. Obviously must be very troubling to you to have provided so many documents to various investigations and not had that among them in the past. Where did you find it?

Ms. PRICE. We found that in an electronic file in a shared drive that was shared by different personnel at Copernicus. And it was not made part of the hard copy file, which is, unfortunately, what we tended to look at mostly during the course of this investigation.

Mr. WALDEN. So you never looked at that drive before when you were producing documents?

Ms. PRICE. No, we didn't look particularly at that drive. We had done electronic searches on the drive and had come up with that document back in 2006 when Senator Grassley requested information about—

Mr. WALDEN. You had come up with that document?

Ms. PRICE. We had—an electronic search had come up with that document at the time that Grassley requested information. However, Grassley's investigation centered on information received 2006 and after.

Mr. WALDEN. OK.

Ms. PRICE. And so that wasn't looked at as part of that.

Mr. WALDEN. OK. So you had—you knew you had that document.

Ms. PRICE. It came up in a search. We hadn't looked at it, you know.

Mr. WALDEN. I see. And you said you had done a thorough investigation on all of this. Did you do a forensics investigation, then, on the computer drive just to make sure, you know, when it was done?

Ms. PRICE. Yes, as part of that investigation was looking at the properties—I think that is what you are referring to, the properties of the document. And it was generated and only touched on one

day, and that was February 22nd, 2002, the day after it was supposedly—the call was supposedly made.

Mr. WALDEN. I think the document actually says the 21st on it.

Ms. PRICE. The document actually says the call was made on the 21st. But the document, according to the properties, was generated on the 22nd.

Mr. WALDEN. Thank you. That helps clear that up.

Dr. Chew, I would like to ask you a couple of brief questions. Do you agree or disagree with the contention of an FDA criminal investigator that Aventis's system for overseeing the clinical trials in the 3014 study was not designed to enable your company to detect criminal fraud?

Dr. CHEW. Congressman Walden, there was a specific process in the former company looking for scientific fraud. And in the case of Dr. Kirkman-Campbell, the teleconference that was alluded to on March 4th, 2002—the minutes were March 6th, but the meeting clearly had as its title “The Discussion of Scientific Misconduct.” And it is my belief, looking back at those records, that the team, both Aventis and PPD, were following the process of trying to look at scientific fraud. And it was clear that the team—in fact, it was an Aventis employee that in January, 17th and 18th, had gone to the site and reviewed 327 informed consents. That was in January, and it was at that charge that PPD was asked to make the February visits—which Ms. Cisneros was there.

So there was an early detection of a potential problem. And the monitoring responsibility was clearly delegated, and where we found out even more issues that needed to be addressed. And these are minuted in the scientific fraud discussion of March 4th.

Mr. WALDEN. What would you do differently today than what was done then? Because it sounds like you are describing for me a system that worked. And yet we know it didn't work.

Dr. CHEW. Well, as I said, I was not involved in the trial.

Mr. WALDEN. Right.

Dr. CHEW. And looking back at the record, and with the benefit of hindsight I wished, for transparency, that the FDA had been called. As you heard this morning, there is really no clear guideline on when to call, short of scientific misconduct. I wish they had been called. I wish Aventis had picked up the phone and said, We have a problem. We can't document it.

What I saw, though, was an enormous amount of resources were spent at Dr. Kirkman-Campbell's site, with over 165 phone calls. I think she had four monitoring visits. Probably more was expended trying to look at that.

And the other problem, and you heard that this morning, is when you do a big trial, 24,000 patients, among physicians who are not used to doing that, frankly, this was the first trial of an antibiotic of that scale done preapproval.

Mr. WALDEN. Why did Aventis take such efforts to bring her into compliance?

Dr. CHEW. Why did Aventis?

Mr. WALDEN. Yeah.

Dr. CHEW. I think as a matter of course when you do monitoring, even though be it by the nature of the program it was retrospec-

tive, is to identify issues, to document issues, and that they were not overlooked.

Mr. WALDEN. Now, we heard earlier that—from I think Mr. Loveland—that basically Aventis brought in mathematicians to do statistical analyses of data that were coming out of a system designed to identify potential fraud. The phone records, the fact that Dr. Campbell was dialing every 50 to 70 seconds. Can you speak to that?

Dr. CHEW. From my review of the record, first of all I think it is—it was identified that there would be a statistical approach to look at the variations in blood samples. Because if there were split blood samples, they might tend to look more alike than normally would occur between people. So that there was an attempt by the statistician. Unfortunately, not enough baseline data was there for his preferred analysis. So what he did was to compare the variability of blood samples at Dr. Kirkman's site with another site. And there was not conclusive data to show that this was a fraudulent blood sample. So that was the purpose of looking statistically at the blood samples.

Mr. WALDEN. Well, do you believe that extensive violation of GCPs in a clinical trial can affect data integrity, even when there is not fraud?

Dr. CHEW. Congressman, we believe that is possibly the case. In this particular case I am talking about Dr. Kirkman-Campbell. What we heard was that it was not so much a question of whether the patients existed, because from my review of the record she randomized 407 patients. I believe there was only one case—of course it is very serious—but I believe there was only one case in which there was a patient made up of whole cloth.

Mr. WALDEN. But didn't she have a lot of patients that didn't fit the requirements for the trial?

Dr. CHEW. The requirements of the trial, in a real-world setting of a real-office practice, was to look at patients who had acute exacerbations of chronic bronchitis, sinusitis, or walking pneumonia, community-acquired pneumonia.

Mr. WALDEN. So all of her patients had that?

Dr. CHEW. Well, she was asked—all investigators were asked to use their clinical diagnosis. It was not required, just like it isn't in the real world, to require—

Mr. WALDEN. So you are not telling me that she diagnosed that all those people on her trial had walking pneumonia or one of the other two issues, right?

Dr. CHEW. It is my understanding that she represented that these patients had the qualifying diagnoses.

Mr. WALDEN. And you say there is only one patient that was made up. Do you think those data, out of the 400 patients, should have been used in this evaluative process?

Dr. CHEW. Well, again looking back, I could see that the data was addressed, it was documented. I think the best efforts were made—I don't think, I don't think—

Mr. WALDEN. There were forgeries, though, weren't there?

Dr. CHEW. There was one alleged forgery.

Mr. WALDEN. What was she convicted of, then?

Dr. CHEW. She was convicted of falsifying clinical records using interstate mail.

Mr. WALDEN. And how many clinical records did she falsify?

Dr. CHEW. I would have to review that.

Mr. WALDEN. Only one?

Dr. CHEW. No, she pled guilty, I believe, to one count, but there were many allegations.

Mr. WALDEN. So you have reviewed all 400 records, and you still only believe there was one that was bad?

Dr. CHEW. From my review of the criminal documents, there was one that was made up out of whole cloth. But there were serious problems with the other patients because—and this is very important—these patients were not properly consented. Many did not know they were participating in a clinical trial. Because the investigators were able to talk to patients. And from my review of the record, sponsors, and, in this case, Aventis, did not talk to patients and inquire about their status.

Mr. WALDEN. Do you have to talk to patients to find fraud?

Dr. CHEW. In this case I think the bulk of the issues were informed consent—the bulk of the issues were involving patients who were not aware.

Mr. WALDEN. That they were in a clinical trial.

Dr. CHEW. That they were in a clinical trial, that they were taking experimental medicine, the reasons their bloods were drawn. That is very serious.

Mr. WALDEN. Do you think Aventis has any liability in a situation like that, since you are responsible for the trials and overseeing them?

Dr. CHEW. Any pharmaceutical company, in particular in this case Aventis, has to submit, to the best of their knowledge, the highest quality data. I don't want to make any ambiguity about that. And they need to submit that with all the due diligence possible. One of the lessons learned, again, was not only could Aventis in retrospect have called, but also they could have put in more documentation in the final study report of gray-area issues, even if fraud had not been actually documented.

Mr. WALDEN. Can you assure the committee that your standard operating procedures today have changed sufficiently that this won't be replicated?

Dr. CHEW. I can assure you, Congressman Walden, that the procedures and the training—we have even brought in the former, I think, deputy head of DSI to talk with and train our people. We have now also made a very big change in the standard operating procedure. Not only is it scientific fraud, but it is serious non-compliance with the GCP that will raise the bar for detection and procedures throughout the company.

Mr. WALDEN. And one final—well, did Dr. Kirkman-Campbell participate in any other Aventis trials?

Dr. CHEW. Yes, she did.

Mr. WALDEN. And have you reviewed that work?

Dr. CHEW. Yes, I have.

Mr. WALDEN. Have you found any problems with any of those data?

Dr. CHEW. To my knowledge this was an insulin trial, with four patients, that was started. She was recruited, to my knowledge, independently of the Ketek team.

Mr. WALDEN. Right.

Dr. CHEW. They were unaware at the time when they included her that there was a problem, but once this was found, when she requested additional patients, the answer was no. And she was shortly thereafter, I think—

Mr. WALDEN. Right. But of those she already had in the other trial, were there any problems with her data?

Dr. CHEW. To my knowledge there were no issues.

Mr. WALDEN. Have you reviewed her data? Do you have any knowledge—

Dr. CHEW. I have not been made aware of any issues. We could provide—

Mr. WALDEN. My question is, Have you reviewed those data?

Dr. CHEW. I have only reviewed issues that have come up with her data. And that was not listed as one of the issues.

Mr. WALDEN. All right. Have you or have you not looked at the data out of the other trial?

Dr. CHEW. In the other trial, I have not looked at her four-patient data.

Mr. WALDEN. All right. So of course you wouldn't have any knowledge that there is a problem there, because you never looked at those data.

Dr. CHEW. I believe—

Mr. WALDEN. That's fair. I am just trying to get an answer.

Dr. CHEW. No, I believe if there had been an issue in the records with Dr. Kirkman-Campbell, with any of her participation, I am confident I would have been made aware.

Mr. WALDEN. So somebody else in your company has looked at those data?

Dr. CHEW. I am confident they have, because this was approximately 2003 we are talking about.

Mr. WALDEN. I will leave it up to the Chairman, but it would be interesting to know for sure. Thank you.

Mr. STUPAK. Ms. Price, you said in response to Mr. Walden's questions that Senator Grassley asked for some documentation there, and you found that memo but you didn't turn it over to Senator Grassley's committee?

Ms. PRICE. No. Senator Grassley requested us to look at a lot of documents. And working with counsel, they determined that the information that they wanted was 2006 onward.

Mr. STUPAK. So you became aware of this document at Senator Grassley's request, right? And this document—

Ms. PRICE. This is on rereview of information.

Mr. STUPAK. Document number 33, right there. Exhibit No. 33.

Ms. PRICE. That's the telephone contact report of February 21.

Mr. STUPAK. At Senator Grassley's request you came across this document, correct?

Ms. PRICE. In review—in review and preparation for the meeting with your staff we became aware—

Mr. STUPAK. No, no. I am asking about Senator Grassley. In your testimony and questions with Mr. Walden, you said you came

across this document when Grassley—when Senator Grassley asked for it, but it was outside the purview of his request; therefore you did not give it to him. Correct?

Ms. PRICE. It was not responsive to his request.

Mr. STUPAK. When was that? That was about a year ago, wasn't it?

Ms. PRICE. That was 2006. That was a year before your hearing.

Mr. STUPAK. 2006. So you have known about this document since 2006, then, the existence of this document.

Ms. PRICE. It appeared on a long listing of thousands of documents.

Mr. STUPAK. Right. And you knew about it in 2006, correct?

Ms. PRICE. That's what our investigation turned up as we were looking into this.

Mr. STUPAK. So then why did you sit on the document until the day before committee staff interviewed you, even though we had the request in for about a year? Why did you sit on it for a year until the day before the interview?

Ms. PRICE. We didn't sit on it.

Mr. STUPAK. What did you do with it, then, for a year?

Ms. PRICE. We were aware of it on an electronic search.

Mr. STUPAK. In 2006 you are aware of it.

Ms. PRICE. Yes, in 2006. We hadn't opened the document in 2006 to look at it because it wasn't in response to what Senator Grassley—

Mr. STUPAK. Sure. So you looked at it and said, This doesn't go for a Senator.

Ms. PRICE. It appears that nobody looked at it.

Mr. STUPAK. How would you know if it was in keeping with Senator Grassley's request, then, if you didn't look at it?

Ms. PRICE. It showed up on an electronic data search. It showed up simply as a telephone contact report. It had a date of when it was written.

Mr. STUPAK. Sure. What was the date it was written?

Ms. PRICE. I would have to look back, but I think that the date—

Mr. STUPAK. And that electronic search would also have the person who entered the information on that document, would it not?

Ms. PRICE. The electronic search did not have an author, I don't believe, on it.

Mr. STUPAK. You don't know or you don't remember?

Ms. PRICE. I don't remember—I don't remember.

Mr. STUPAK. Is that a computerized form right there, Exhibit No. 33? Is that a computerized form?

Ms. PRICE. Yes, it is. It is a Word document.

Mr. STUPAK. So your backup files would have when it was entered and by whom, would it not?

Ms. PRICE. Yes. That's why it turned up on the electronic search. When we narrowed down our search criteria to—

Mr. STUPAK. Sure. So your electronic search would have who entered it, then, correct?

Ms. PRICE. The electronic search that I remember seeing did not have who entered it, no.

Mr. STUPAK. So you have a document retention policy, do you, at your organization, at your company?

Ms. PRICE. Yes, we do.

Mr. STUPAK. OK. So can you provide us with that electronic search log which indicates this document was a part of it?

Ms. PRICE. I would be happy to.

Mr. STUPAK. OK. I am going to ask you this. The telephone document—I should say telephone contact—indicates that Sarah Wallace took the report, right?

Ms. PRICE. Yes, sir.

Mr. STUPAK. But the testimony has been that Ms. Cisneros talked to you. Correct?

Ms. PRICE. That was her initial testimony.

Mr. STUPAK. And that was her testimony this morning, too.

Ms. PRICE. Today she said she thought she spoke to the President.

Mr. STUPAK. Right. And she identified you as the President, right?

Ms. PRICE. She did not identify me as the President until after you asked her who the President was.

Mr. STUPAK. Right. So she identified you as the President. OK. And you are claiming you never talked to her.

Ms. PRICE. That's correct. I never talked to her.

Mr. STUPAK. What is your company's policy on filling out this form here, this telephone contact form? Is it supposed to be done when the contact was made, or do you do it the next day? What was your company policy on filling out this document?

Ms. PRICE. At the time, the company policy was to fill out telephone contact reports for any significant issues. And obviously, Sarah Wallace felt this was significant enough to fill out a telephone contact.

Mr. STUPAK. Right. Is there a time frame when she is supposed to fill out this contact?

Ms. PRICE. There was no timeframe given in our—

Mr. STUPAK. So she could do it a week later if she felt compelled to do it a week later?

Ms. PRICE. Yes, but she had been trained to do it soon after the call.

Mr. STUPAK. Who trained her to do it soon after the call?

Ms. PRICE. Training at that point was done by our Director of IRB Services and/or myself and other experienced professionals.

Mr. STUPAK. OK. And Ms. Wallace left Copernicus shortly after this call was received. Is that correct?

Ms. PRICE. Yes, she did. Within 2 weeks, I believe.

Mr. STUPAK. And in an interview with Ms. Wallace, she stated to committee staff she did not remember getting this call, but she was certain that if she had gotten the call she would have immediately notified you or Dawn Pope because of the extraordinary content of the call.

Do you think she would have contacted you if she would have received the call?

Ms. PRICE. She must have told you all that, yes. And I feel that it is highly unusual to get a call like this, and she would have remembered to forward that on to her supervisor.

Mr. STUPAK. OK. So who had been her supervisor then?

Ms. PRICE. Our Director of IRB services.

Mr. STUPAK. Who is that?

Ms. PRICE. Dawn Pope.

Mr. STUPAK. OK. Did Dawn Pope ever talk to you about receiving this call or the information she received from Sarah Wallace?

Ms. PRICE. No, sir.

Mr. STUPAK. So what happens to this information when serious allegations like this are made? What would happen if you would have been informed? What would have happened?

Ms. PRICE. This type of call should have been forwarded to a supervisor, and then would have eventually gotten to the Institutional Review Board, where it would have been investigated and action taken by the Board.

Mr. STUPAK. So did you talk to Ms. Pope about whether or not she ever received this document?

Ms. PRICE. Certainly, yes.

Mr. STUPAK. And what is her response?

Ms. PRICE. She does not remember this either.

Mr. STUPAK. So Ms. Wallace just filled out this form and it sat in your files?

Ms. PRICE. It appears so. It appears to be a human error, and I wish I could explain it, but I cannot.

Mr. STUPAK. Well, who would—does it indicate who she forwarded that to, Ms. Wallace—does it indicate who Ms. Wallace forwarded it to?

Ms. PRICE. No.

Mr. STUPAK. Would your electronic file indicate who she forwarded it to?

Ms. PRICE. Excuse me?

Mr. STUPAK. Would your electronic files show who she would have forwarded it to?

Ms. PRICE. I don't know the answer to that. I would have to find out. But I think that we looked to see if it had ever been printed, because that was one of our concerns, too. This should have been not only generated, but also printed and put in the investigator hard-copy file.

Mr. STUPAK. OK. So what happened? Did a hard copy go into the investigative file then?

Ms. PRICE. No, it did not. And that was where the rub was. It should have gone into the file.

Mr. STUPAK. So this serious allegation went to your organization and it just sat there. Never forwarded it, no hard copies ever made, nothing.

Ms. PRICE. That's correct.

Mr. STUPAK. Would Ms. Wallace know to make a hard copy and put it in the file?

Ms. PRICE. Would Ms. Wallace what? Excuse me?

Mr. STUPAK. Ms. Wallace would have made a hard copy, right?

Ms. PRICE. The person who took the call would have normally—

Mr. STUPAK. That's what she should have done?

Ms. PRICE. Yes, sir.

Mr. STUPAK. So—OK. Do you know how many protocol violations or deviation forms you received on Study 3014.

Ms. PRICE. On the entire Study 3014?

Mr. STUPAK. Yes.

Ms. PRICE. No, but there were quite a few memos to file.

Mr. STUPAK. What did you do with the information then? You had quite a few complaints about Study 3014. What did you do with the information?

Ms. PRICE. Our policy at the time was to not review protocol violations. We were concentrating on serious adverse events that were reported by the investigators for the study.

Mr. STUPAK. So you are saying your violations that you heard of were only protocol violations and not serious adverse events. Right?

Ms. PRICE. That was our procedure at the time. We have now certainly changed that.

Mr. STUPAK. So protocol violations, no matter the number, wasn't alarming to your organization, to Copernicus?

Ms. PRICE. Not at the time, no. We felt that those were things that were picked up on the monitoring visits and were corrected at the site—with the site at that time.

Mr. STUPAK. How do you know if they were corrected? You said you assumed they were corrected. How do you know that?

Ms. PRICE. In some cases it is an assumption, in some cases the actual memo to file did indicate that there was reeducation of the investigators.

Mr. STUPAK. Turn to Exhibit 32, if you would, in the book there. This document is entitled procedure number 108. It reflects the procedures at Copernicus with respect to safety and noncompliance reporting requirements. Correct?

Ms. PRICE. Yes, that's correct.

Mr. STUPAK. OK. Were you under duty to notify the IRB when you received protocol violations? Isn't that what it says?

Ms. PRICE. Under duty to inform the IRB of protocol violations?

Mr. STUPAK. Sure. Sure.

Ms. PRICE. Let me take a look here and see—do you know which number it's addressed in?

Mr. STUPAK. Number 6.

Ms. PRICE. The Board is responsible for reporting investigator noncompliance as required by applicable Federal regulations.

Mr. STUPAK. Sure. So were you required to notify the IRB when you received protocol violations?

Ms. PRICE. Our interpretation of the regulations at that point did not constitute us reporting protocol violations to the Board.

Mr. STUPAK. So now you believe you are required to do so?

Ms. PRICE. We have evolved a lot in 6 years as an Institutional Review Board, as has the industry, and now require the investigators to report unanticipated problems. And that's what this would have arisen to.

Mr. STUPAK. So when did Copernicus start, then? When did your company start? When did you start? You said you founded the company. When did you do that?

Ms. PRICE. 1996, sir.

Mr. STUPAK. 1996. So you are in 6 years since when you started seeing the problems, then, with Kirkman-Campbell, right?

Kirkman-Campbell, 2002, when you were doing this work here for Aventis and all that, correct?

Ms. PRICE. We became IRB of record, or were asked to be IRB of record in 2001.

Mr. STUPAK. OK. But in 1996 you had been an IRB, right?

Ms. PRICE. Yes, we started in 1996.

Mr. STUPAK. So you had more than one IRB before 2001, right?

Ms. PRICE. We had one—I don't understand your question.

Mr. STUPAK. OK. You said you were asked to be an IRB in 2001. Correct?

Ms. PRICE. For 3014, yes, sir.

Mr. STUPAK. But before that, you had been an IRB before, right? Since 1996 you had served as an IRB.

Ms. PRICE. Yes.

Mr. STUPAK. So you certainly knew the requirements. If you didn't know the understanding of procedure number 8 or paragraph number 6 there, entitled Procedure Number 108 reflects procedures of Copernicus with respect to safety and noncompliance reporting requirement, why would you have it if you didn't understand what it meant? It is your own procedures.

Ms. PRICE. We did understand what it meant at the time. The interpretation was protocol violations did not constitute serious adverse events or unanticipated problems. The whole industry has evolved since then. And we feel that we have systems in place now and policies and procedures that would address this.

Mr. STUPAK. So this one case, this Study 3014, has changed the whole industry standard on the way you do things?

Ms. PRICE. No, sir. There has been an evolution going on for a long time, and I think the area of unanticipated problems is certainly one that we deal with constantly. As late as April 2007 there has been some draft guidance from FDA regarding what needs to be submitted to the IRB and what would constitute an unanticipated problem.

Mr. STUPAK. How many memos to the file or protocol violations did you receive just regarding the Kirkman-Campbell site alone?

Ms. PRICE. We received 83, I believe, 83 memos to file of protocol violations, and we received them 3 months after she closed as an investigator.

Mr. STUPAK. So you received 83 different complaints. Given the number and nature of the informed consent and other violations, didn't you have an obligation to ensure patient safety at these sites, or at least inquire from the sponsor to see what was taking place?

Ms. PRICE. We had no authority after she was closed to do anything about it. And no, we did not report them to the FDA.

Mr. STUPAK. OK. Well, I have got plenty more questions, but Senator Grassley is here. So I think we are going to suspend this panel for now. We will ask you to stay.

Senator Grassley would like to testify. And we will accommodate the Senator. We are going to have him come up and testify.

Mr. MARKEY. Mr. Chairman?

Mr. STUPAK. Yes.

Mr. MARKEY. May I be recognized?

Mr. STUPAK. No. We are going to do the courtesy to Senator Grassley. He is going to testify.

Mr. MARKEY. Oh, I am sorry.

Mr. STUPAK. And this panel will be back, so you will have a chance to ask questions. I didn't mean to cut you short, but we want to get the Senator in.

Mr. STUPAK. Senator, welcome. It is the policy of this committee to take all testimony under oath. I am sure you are not represented by counsel, sir? No? I will ask you to rise and take the oath.

[Witness sworn.]

Mr. STUPAK. Senator, you are now under oath. I would ask you to give your opening statement, please, sir.

**OPENING STATEMENT OF THE HON. CHARLES GRASSLEY, A
UNITED STATES SENATOR FROM THE STATE OF IOWA**

Senator GRASSLEY. OK. I thank you very much for the invitation to come and testify.

Mr. STUPAK. Senator, you want to turn your mike on?

Senator GRASSLEY. It is not on. OK. Thank you.

I thank you very much for the opportunity to be here. Thank you for your leadership in this area. Thank you for your investigation.

I am going to limit my remarks to my work on what is called Study 3014. And that involves the safety of the drug Ketek. It has been a long road, and it still is not at an end.

More than 2 years ago, in January 2006, the journal *Annals of Internal Medicine* reported three cases of liver damage in North Carolina patients who took Ketek. In response, the FDA issued a public health advisory. After all, suffering severe liver problems is quite a price to pay for taking an antibiotic that was being used for such conditions as sinus infections, until that indication was removed from the Ketek label a year ago.

Soon after I heard allegations and concerns regarding the FDA's review of Ketek, and I started asking questions. One of the more serious allegations was that the maker of Ketek, Aventis at the time, submitted clinical trial data to the FDA in support of approval, knowing it was fraudulent.

So I asked FDA to make arrangements immediately for my staff to review documents related to Study 3014 at the FDA's office. Initially, FDA gave my staff access and agreed to provide copies of documents my staff identified during their review.

But then I asked for Special Agent Robert West from the FDA's Office of Criminal Investigation, and the FDA then pulled a 180 on me. I had good reasons for asking for Agent West and being able to question him. One of the other allegations I received was that despite Agent West's concerns and recommendations, FDA never expanded its investigation to determine if the company did, quote-unquote, knowingly submit fraudulent data.

Agent West played an integral role in the investigation of Study 3014, and I am delighted to see that he will be testifying before your committee today, if he hasn't already.

Agent West was the lead agent on the investigation of Dr. Ann Kirkman-Campbell, one of the principal clinical investigators for Study 3014. And as a result of that investigation, Dr. Kirkman-Campbell is currently serving a 57-month prison sentence.

Agent West also was in frequent communication with FDA consumer safety officers and reviewers involved in Study 3014 inspections. But as I testified before this subcommittee a year ago, FDA and HHS wouldn't make Agent West available, even after I went over to the HHS offices to ask personally to speak with Agent West and subpoenas were issued. After all, if FDA had nothing to hide about how it handled Study 3014, why stop me from talking to Agent West?

Obviously, not being able to talk to him at that point, I smelled a cover-up; in fact, even before then.

Well, I now have a better understanding of why FDA did not want me to speak to Agent West regarding Ketek. The answer to the "why" question is equally interesting. It seems to me that there were definitely reasons why the FDA did not want me to meet Agent West, or any other agents for that matter. FDA, it appeared, did not want anyone to know that it didn't further investigate whether or not Aventis submitted fraudulent data knowingly to the FDA. The FDA did that even though Agent West recommended in the summer of 2003, almost 5 years ago now, to high-level officials at the FDA that it needed to create a mini-task force to look into Aventis.

When HHS and FDA finally made Agent West available a short time ago, and that was 18 months after I first requested him, Agent West confirmed that no one acted on his recommendations. In fact, I learned from HHS more than a year after my visit to the Department that the FDA didn't open an investigation into the company until March 2006. Interestingly, that was about the same time that I started poking around the Ketek issue itself.

Agent West told his supervisors, FDA investigators involved in the Study 3014 inspections, as well as FDA directors overseeing the review of Ketek what he thought needed to be inspected; in other words, inspect all of the study sites that enrolled over 100 patients. The protocol for Study 3014 had recommended a maximum enrollment of 50 patients per site, so that that would have meant inspections of about 70 sites.

Agent West's supervisors told my staff that they supported him. The site investigators also thought that it was a good idea.

So then what happened? The head of the Office of Criminal Investigations told my staff that Agent West's concerns and recommendations were referred up the food chain, and he assumed the matter would be taken care of. The Associate Commissioner of Regulatory Affairs at that time said he was prepared to offer any assistance, if needed, but never heard anything more from the Office of Criminal Investigations.

One of Agent West's superiors said that the Center for Drug Evaluation and Research folks were briefed, so the ball was then in their corner. He also said that Agent West's task force proposals had nothing to do with concerns about Aventis.

But I have since learned that that was not true. Agent West sent an e-mail July 2003 to his superiors about his conversation with directors in the Federal FDA Center for Drug Evaluation and Research. These directors oversaw the review of Ketek. In that e-mail, Agent West said, quote, I told them that it was my opinion that

Aventis's new sites were suspect, and did nothing to prove or refute their suspicions, end quote.

Agent West was not the only agent who believed that the company, or at least someone within the company, knew that there were serious problems, particularly at Dr. Kirkman-Campbell's site.

You have the two agents here today who were assigned to the criminal investigation that was opened in March 2006, Special Agents Robert Ekey, and Douglas Loveland. Agent Ekey said, during a joint interview with our committees, that he thought the company too easily dismissed the concerns that were raised by his own contract research organization, the organization that was hired for the specific purpose of monitoring Study 3014.

Agent Loveland wrote in an internal e-mail dated April 17th, 2007 that the company knew significant issues existed at many sites, yet the company submitted the data to the FDA and claimed the study was conducted according to good clinical practices. He also told my staff during an interview yesterday that Aventis should have known there were problems with the integrity of the study data.

The case was closed July 2007. FDA issued a warning letter in October to the company for failing to ensure proper monitoring of Study 3014 and not adequately investigating allegations of fraud at Dr. Kirkman-Campbell's site. The letter cited many of the same problems that FDA staff raised back in 2003 and 2004. So why wasn't the investigation initiated at that time?

Agent West stated in his July 2003 e-mail, quote, I think the three individuals in CDER understood my feelings and opinions, but I don't know whether or not the necessary steps will be accomplished, end quote. When my staff spoke with the three directors, one of them told my staff that if the Office of Criminal Investigation wanted additional investigations, it was their call, not CDER's. He also said that the Office of Criminal Investigations should have talked to the Division of Scientific Investigations, since the division oversees clinical trial site inspections.

So who was responsible? Everyone seemed to be pointing a finger at somebody else, with the exception of the head of the FDA's Office of Division of Special Investigations. This FDA employee told my staff that as far as additional inspections went, they didn't have the resources to do more. And besides, she said, one, the FDA didn't rely on Study 3014 for approval. Two, FDA completed eight site inspections for Study 3014, which is many more than the one or two it normally does. And three, astonishingly, she also said that investigating drug companies is a, quote-unquote, losing game, and the chances of getting a warning letter seemed to be near zero.

I find that attitude, as you should, extremely troubling. We rely on the FDA to ensure that the drugs in our medicine cabinets are safe and effective. That includes FDA making sure that the data supporting the safety and efficacy of the drug is sound. To do that adequately, FDA has to do its job of oversight over clinical trials.

Data integrity isn't the only issue of concern here. FDA also has an obligation to protect human subjects. In December I raised this matter with Commissioner von Eschenbach in a lengthy letter re-

garding my Ketek investigation. That letter, I have been told, is included in your exhibit books.

I asked Commissioner von Eschenbach if it is FDA's position that no additional inspections are required once a study is no longer useful for regulatory action. Then how can FDA protect research subjects from the harm that may be caused by clinical investigators? Not relying on a study for approval does not absolve FDA of its responsibility to protect the individuals who courageously volunteer in clinical trials so that we can all benefit from life-saving cures and medical innovations. I am still waiting for the Commissioner's comments on this very important matter.

Of course, this responsibility does not lie only with the FDA. Of course this responsibility goes beyond FDA. The drug companies also have a responsibility to the people who participate in their clinical trials. They also need to ensure that problems are adequately investigated and addressed.

In the case of Study 3014, there were many sirens, red flags, bullhorns, but it looks like the company and the FDA kept ear plugs in and blinders on.

I would like to close with this. There is something that strikes me as ironic about the case involving Ketek and another investigation involving Dr. Victoria Hampshire, an employee of the FDA. Today we heard a lot about the missteps made by FDA and Aventis. The culmination of these missteps led to a warning letter being sent to Aventis, as opposed to potentially more serious action being taken.

And then we have the case of Dr. Hampshire, where the FDA worked mightily to pursue her. In fact, the FDA went so far as to send a criminal referral to the United States attorney in Maryland to prosecute her for alleged wrongdoing. Disturbingly, the FDA wrote a criminal referral that was riddled with inaccuracies about Victoria Hampshire. Perhaps in the future the FDA would pursue alleged bad behavior by corporations with the same vigor, same persistence and creativity, with which it pursued Victoria Hampshire.

So, if there are no objections, I would request that my letter to Dr. von Eschenbach about the intensive investigation done by the FDA against one of its own, meaning Victoria Hampshire, be placed into the record.

Mr. STUPAK. Without objection, it will be part of the record.

[The information appears at the conclusion of the hearing.]

Senator GRASSLEY. So I thank you for your invitation and your patience with my schedule today, because we had nine votes on the Senate floor that kept me from being here at the appropriate time. I would like to not take questions, if that is possible.

Mr. STUPAK. That is possible. Would you take a question from Mr. Dingell?

Senator GRASSLEY. I will take questions.

Mr. STUPAK. Mr. Dingell, do you have a question for Senator Grassley?

Senator GRASSLEY. When you say I learned all my oversight work from him, how could I ignore him?

Mr. STUPAK. I agree. I agree. Go ahead.

Mr. DINGELL. You are very kind, Mr. Chairman. I was waiting to hear your questions.

Mr. STUPAK. Senator Grassley is on a tight schedule, so I would defer to the full Chairman for any questions.

Mr. DINGELL. Then let me first welcome Senator Grassley. It is wonderful to see my old friend back here. Welcome back to the House, where you started. And it is a pleasure to see you in this room again, where we have done great work together, you and I, and I am very proud of your labors.

So I will give you questions that in view of your time constraint, I think most of these will be answerable "yes" or "no."

Senator, from your testimony today and that which you graciously provided this committee a year ago, I take it you believe FDA and the Department of HHS have been extraordinarily uncooperative in your inquiry into the matter. Is that correct?

Senator GRASSLEY. The answer is yes, and I think Agent West is the best example of that.

Mr. DINGELL. Now, I note that lack of cooperation, including defying one or more lawful subpoenas issued by you as Chairman of the Senate Finance Committee. Is that correct?

Senator GRASSLEY. We have had difficulty getting those responses even with a subpoena. And again, Agent West is an example.

Mr. DINGELL. That related both to appearances of personnel and also production of papers. Is that correct?

Senator GRASSLEY. Very true.

Mr. DINGELL. I take it that you still have serious questions as to exactly what the Department wished to avoid revealing to your committee. Do you agree that FDA has been forthcoming with the public regarding the safety of this drug Ketek?

Senator GRASSLEY. Very definitely.

Mr. DINGELL. So now, FDA, after acknowledging that the pivotal safety study for Ketek was full of clinical fraud, approved the drug anyway, claiming there were insufficient adverse events reported in countries such as Italy and Brazil to prove that it was not safe. Is that correct?

Senator GRASSLEY. Well, that's correct from the standpoint that I think that those are things that Agent West pointed out that needed to be further investigated. I am not sure that I can speak to the points about the other countries that you made mention of. But basically, I am referring now to my staff, and they said basically the answer is yes.

Mr. DINGELL. And it doesn't make sense to you, does it?

Senator GRASSLEY. No, obviously not. I hope my testimony made very clear that I am incensed that, when we are doing our constitutional job of oversight, that we don't get the cooperation from the executive branch of government.

Mr. DINGELL. Now, I believe it is sort of the fact, the rule of thumb in the United States is that only about 10 percent of adverse events get reported. Is that right?

Senator GRASSLEY. Approximately. Yes.

Mr. DINGELL. Now, Senator, in fact, has FDA ever before or since made a safety determination for a new drug primarily on the basis

of the lack of adverse event data in the United States, much less in countries such as Brazil and Italy?

Senator GRASSLEY. I think I will have to take a pass on that question. I am not sure I can answer that.

Mr. DINGELL. It is my understanding that this is unprecedented.

Senator GRASSLEY. OK.

Mr. DINGELL. Would it be fair to say that the FDA officials that approved this drug discouraged information from their own investigators, and those were investigators trained both in the detection of scientific misconduct and criminal fraud, in an attempt to get the advisory committee reviewing the data from the fraudulent study to recommend approval?

Senator GRASSLEY. The answer is yes, and that is a fair summary of some of the points I was trying to make.

Mr. DINGELL. Now, Senator, did Aventis inform the advisory committee of data problems? Much less did they inform them of the existence of a fraud investigation when they presented the Study number 3014, the pivotal study in January 2003?

Senator GRASSLEY. The answer is no.

Mr. DINGELL. Do you believe that the field investigators, when they were allowed to do their jobs, worked diligently and competently to uncover wrongdoing at Aventis?

Senator GRASSLEY. The answer is yes. And I refer specifically to Agent West that I worked so hard to get in contact with, but also others as well. But the others my staff were more involved with.

Mr. DINGELL. Now Senator, do you believe that the primary reviewers, the whistle-blowers that came to your committee and testified here last year, raised appropriate concerns about the safety and efficacy of Ketek?

Senator GRASSLEY. Of course. They are a major source of information on this specific case. But I want to point out, to encourage whistle-blowers everywhere in government, that they are a very important part of the process of congressional oversight. We can't know where all the skeletons are buried, and we want to find out where those skeletons are, not just in this administration but every administration in the past when it has been difficult, and in the future.

Mr. DINGELL. We happen to agree very strongly on that, Senator.

Now, if the investigators did a good job in detecting problems and the reviewers did a good job in assessing their implications, what does this say about the supervisors in CDER, that is the Center for Drug Evaluation and Research?

Senator GRASSLEY. Well, it seems to me that they were not doing their job.

Mr. DINGELL. It seems to be very clear from the record here.

Now, Senator, you referred to Dr. Victoria Hampshire. And you have indicated that she is essentially a whistle-blower who is now being, quite frankly, inquired into in ways that I think you indicated are less than fully correct by FDA and by the Justice Department and others.

Senator GRASSLEY. Yeah, and by a company that worked with FDA to implicate her.

Mr. DINGELL. Would you want to tell us a little bit more about that?

Senator GRASSLEY. Well, for instance, we know of an instance in which there was a PowerPoint program put together to come in to show why Dr. Hampshire ought to be fired.

Mr. DINGELL. I think we will be asking for that.

Senator GRASSLEY. Would you please contact my staff in regard to the details of that?

Mr. DINGELL. I would certainly do so.

I wanted to ask you, Senator, because I think this is an important question, you did a superb job as Chairman of the Finance Committee and we have much to thank you for for your labors on this particular matter. Would you suggest that this committee ought to have a look maybe at the behavior of FDA with regard to Dr. Hampshire?

Senator GRASSLEY. I would. It would be very helpful, because you as the Chairman will get the attention much more than a Ranking Member, even considering I am in the higher body.

Mr. DINGELL. We will try and get their attention. And I think working together we can perhaps procure some more focused and proper care, concern and attention at FDA. Senator, it is a privilege to see you again.

Mr. STUPAK. Thank you, Senator.

Mr. DINGELL. And thank you for your courtesy to me, Mr. Chairman.

[The prepared statement of Senator Grassley follows:]

STATEMENT OF SENATOR CHUCK GRASSLEY

Chairmen Dingell and Stupak, Ranking Members Barton and Shimkus, and distinguished colleagues, thank you for inviting me to speak today about my investigation of FDA's handling of the large safety study Ketek, Study 3014. It has been a long road and it's still not at an end.

More than two years ago, in January 2006, the journal *Annals of Internal Medicine* reported three cases of liver damage in North Carolina patients who took Ketek. In response the FDA issued a public health advisory.

After all, suffering severe liver problems is quite a price to pay for taking an antibiotic that was being used for such conditions as sinus infections until that indication was removed from the Ketek label a year ago.

Soon after, I heard allegations and concerns regarding FDA's review of Ketek and I started asking questions. One of the more serious allegations was that the maker of Ketek, Aventis at the time, submitted clinical trial data to the FDA in support of approval, knowing it was fraudulent.

So I asked FDA to make arrangements immediately for my staff to review documents related to Study 3014 at the FDA's offices.

Initially, FDA gave my staff access and agreed to provide copies of documents my staff identified during their review.

But then I asked for Special Agent Robert West from FDA's Office of Criminal Investigations and the FDA pulled a 180 on me.

I had good reasons for asking for Agent West. One of the other allegations I received was that despite Agent West's concerns and recommendations, FDA never expanded its investigation to determine if the company did "knowingly" submit fraudulent data.

Agent West played an integral role in the investigation of Study 3014 and I am delighted to see that he will be testifying on the next panel along with two other special agents from the agency. Agent West was the lead agent on the investigation of Dr. Anne Kirkman Campbell, one of the principal clinical investigators for Study 3014. And as a result of that investigation Dr. Kirkman Campbell is currently serving a 57-month prison sentence. Agent West also was in frequent communication with the FDA consumer safety officers and reviewers involved in the Study 3014 inspections.

But as I testified before this subcommittee a year ago, FDA and HHS wouldn't make Agent West available-even after I went over to the HHS offices to ask person-

ally to speak with Agent West and subpoenas were issued. After all, if FDA had nothing to hide about how it handled Study 3014, why stop me from talking to Agent West? I smelled a “cover-up.”

Well, I now have a better understanding of why FDA did not want me to speak to Agent West regarding Ketek. The answer to the “WHY” question is equally interesting. It seems to me that there were definitely reasons why the FDA did not want me to meet with Agent West or any other agents for that matter. FDA, it appears, did not want anyone to know that it didn’t further investigate whether or not Aventis submitted fraudulent data knowingly to the FDA. The FDA did that even though Agent West recommended, in the summer of 2003—almost 5 years ago—to high level officials at the FDA that it needed to create a mini-task force look into Aventis.

When HHS and FDA finally made Agent West available a short time ago—18 months after I first requested him—Agent West confirmed that no one acted on his recommendations. In fact, I learned from HHS more than a year after my visit to the Department, that the FDA didn’t open an investigation into the company until March 2006. Interestingly, that was around the same time I started poking around Ketek.

Agent West told his supervisors, FDA investigators involved in the Study 3014 inspections, as well as FDA directors overseeing the review of Ketek what he thought needed to be done—inspect all the study sites that enrolled over 100 patients. The protocol for Study 3014 had recommended a maximum enrollment of 50 patients per site, so that would have meant inspections of about 70 sites.

Agent West’s supervisors told my staff that they supported him. The site investigators also thought it was a good idea. But what happened?

The head of the Office of Criminal Investigations told my staff that Agent West’s concerns and recommendations were referred up the food chain, and he assumed the matter would be taken care of.

The Associate Commissioner for Regulatory Affairs at that time said he was prepared to offer any assistance if needed but never heard anything more from the Office of Criminal Investigations.

One of Agent West’s superiors said the CDER folks were briefed so the ball was in their court. He also said that Agent West’s task force proposal had nothing to do with concerns about Aventis.

But I have since learned that that’s not true.

Agent West sent an email in July 2003 to his superiors about his conversation with directors in FDA’s Center for Drug Evaluation and Research. These directors oversaw the review of Ketek.

In that email, Agent West said, “I told them that it was my opinion that Aventis knew sites were suspect but did nothing to prove or refute their suspicions.”

Agent West was not the only agent who believed that the company or at least someone within the company knew there were serious problems, particularly at Dr. Kirkman Campbell’s site. You have the two agents here today who were assigned to the criminal investigation that was opened in March 2006—Special Agents Robert Ekey and Douglas Loveland.

Agent Ekey said during a joint interview with our Committees that he thought the company too easily dismissed the concerns that were raised by its own contract research organization, the organization hired to monitor Study 3014.

Agent Loveland wrote in an internal email dated April 17, 2007, that the company knew significant issues existed at many sites yet the company submitted the data to the FDA and claimed the study was conducted according to good clinical practices. He also told my staff during an interview yesterday that Aventis should have known that there were problems with the integrity of the study data.

The case was closed in July 2007. FDA issued a warning letter in October to the company for failing to ensure proper monitoring of Study 3014 and not adequately investigating allegations of fraud at Dr. Kirkman Campbell’s site. The letter cited many of the same problems that FDA’s staff raised back in 2003 and 2004. So why wasn’t an investigation initiated then?

Agent West stated in his July 2003 email, “I think the three individuals in CDER understood my feelings and opinions but I don’t know whether or not the necessary steps will be accomplished.”

When my staff spoke with the three directors, one of them told my staff that if the Office of Criminal Investigations wanted additional investigations, it was their call, not CDER’s. He also said that the Office of Criminal Investigations should have talked to the Division of Scientific Investigations since the division oversees clinical trial site inspections.

So who’s responsible?

Everyone seemed to be pointing the finger at someone else, with the exception of the head of FDA's office of Division of Scientific Investigations. This FDA employee told my staff that as far as additional inspections went, they didn't have the resources to do more. And besides, she said (1) the FDA didn't rely on Study 3014 for approval, (2) FDA completed 8 site inspections for Study 3014, which is many more than the one or two it normally does, and (3) astonishingly, she also said that investigating drug companies is a "losing game" and the chances of getting a warning letter is zero.

I find that attitude extremely troubling, as I'm sure you do as well.

We rely on the FDA to ensure that the drugs in our medicine cabinets are safe and effective. That includes FDA making sure that the data supporting the safety and efficacy of a drug is sound. To do that adequately, FDA has to do its job of oversight over clinical trials. Data integrity isn't the only issue of concern here. FDA also has an obligation to protect human subjects.

In December, I raised this matter to Commissioner von Eschenbach in a lengthy letter regarding my Ketek investigation. That letter I've been told is included in your exhibit books. I asked Commissioner von Eschenbach: If it is FDA's position that no additional inspections are required once a study is no longer useful for regulatory action, then how can FDA protect research subjects from the harm that may be caused by clinical investigators?

Not relying on a study for approval does not absolve FDA of its responsibility to protect the individuals who courageously volunteer in clinical trials so that we can all benefit from lifesaving cures and medical innovation. I am still waiting for the Commissioner's comments on this important matter.

Of course, this responsibility does not lie only with the FDA. The drug companies also have a responsibility to the people who participate in their clinical trials. They also need to ensure that problems are adequately investigated and addressed.

In the case of Study 3014, there were sirens, red flags and bull horns, but it looks like the company and the FDA kept ear plugs and blinders on.

I like to close by saying that it troubles me that the FDA failed to act on the serious concerns raised by Agent West until almost 2 years after Ketek was approved and almost 3½ years after Study 3014 was submitted to the FDA. It troubles me that an FDA manager would say that investigating a company is a "losing game" because in the case of Ketek, after the FDA did do the investigation, a warning letter was issued. This same individual, however, has also said that more oversight of clinical trials was needed.

FDA officials have told me that some initiatives are underway, including making sure that there's proper oversight and authority over all the parties involved in clinical trials. I hope we see significant improvements in the near future.

There's also been a lot of talk over the last several months about FDA inspections, especially foreign inspections. FDA has limited resources to perform this important function. Just as more and more drugs are being manufactured overseas, more and more studies are being conducted outside of the United States.

I look forward to working with this Committee and in particular with you, Chairmen Dingell and Stupak and Ranking Members Barton and Shimkus, as well as my colleagues in the Senate to ensure that FDA has the resources and tools to do its job.

Thank you.

Mr. STUPAK. Let's call back our last panel that was up there. Third panel, Dr. Paul Chew, Dr. Fred Eshelman, and Ms. Sharon Hill Price.

Dr. Chew, Dr. Eshelman and Ms. Sharon Hill Price, you are remaining under oath, understood? OK.

Ms. Price, let me ask you this. What is the purpose of an IRB? What is the main focus of an IRB?

Ms. PRICE. An Institutional Review Board, or IRB as it is called, review clinical research within an ethical and regulatory framework to assure—

Mr. STUPAK. To protect—

Ms. PRICE. Yeah, to assure subject protection according to regulation.

Mr. STUPAK. Assure patient safety.

Ms. PRICE. Subject safety, yes.

Mr. STUPAK. OK. So if there was a concern about patient safety, instead of PPD, the contract review organization, they would go to the IRB, correct?

Ms. PRICE. We are one of the venues, yes, if there is concern about subject safety.

Mr. STUPAK. What other venue is there?

Ms. PRICE. I think subject safety is a shared responsibility, as I indicated in my opening statement.

Mr. STUPAK. With the IRB, Copernicus in this case on Study 3014, and who else?

Ms. PRICE. The sponsor, the investigator.

Mr. STUPAK. That would be Aventis.

Ms. PRICE. The investigator.

Mr. STUPAK. That would be Dr. Kirkman-Campbell.

Ms. PRICE. And the FDA.

Mr. STUPAK. The FDA.

Ms. PRICE. Even the subject to some extent needs to take some responsibility for participating in research.

Mr. STUPAK. Sure. But the main focus, the reason why IRBs came about was to protect patient safety. Correct?

Ms. PRICE. Yes.

Mr. STUPAK. And that is the genesis of the IRB, is patient safety?

Ms. PRICE. Yes.

Mr. STUPAK. OK. And you said you had 83 complaints when I was asking you questions before just on Kirkman-Campbell, right?

Ms. PRICE. Yes, we had 83 memos to file submitted 3 months after she closed.

Mr. STUPAK. Right. And you said it was 90 days after Kirkman-Campbell closed out her work on Study 3014. Correct?

Ms. PRICE. Correct.

Mr. STUPAK. Did you ever read any of those 83 memos that came to the file?

Ms. PRICE. Only recently.

Mr. STUPAK. So while 83 memos came in, you weren't curious to see what the violations were?

Ms. PRICE. They were in a file with 3,300 other investigators, and, at the time, our policy and procedures was not to review those protocol deviations.

Mr. STUPAK. Well, how do you ensure patient safety then if you don't know what the memos and violation are saying.

Ms. PRICE. It was not our policy at the time to review those.

Mr. STUPAK. But isn't that why an IRB comes in fruition? Isn't that why they were created, was to protect patient safety? You get 83 memos in and you don't look at them?

Ms. PRICE. That was our policy at the time. And we have since revised that.

Mr. STUPAK. Well, why would Aventis or anyone hire an IRB if it wasn't to have patient safety as their goal and their mission?

Ms. PRICE. The regulations require the review of clinical research by an institutional review board.

Mr. STUPAK. Right. Its main purpose is patient safety?

Ms. PRICE. Correct.

Mr. STUPAK. So why would anyone hire Copernicus if you're reviewing the files?

Mr. DINGELL. Would you yield? I just wanted to note that I very much appreciate this hearing and I very much appreciate the work you're doing here in this matter and I'm listening most attentively to the matters you're discussing.

Mr. STUPAK. Well, thank you. Well, are you not as an IRB, Copernicus, are you not responsible for reporting noncompliance to the FDA?

Ms. PRICE. Yes, we are. According to our—

Mr. STUPAK. You may want to wait a minute here. It's going to ring for a second. OK.

Ms. PRICE. Issues that rise to the level of noncompliance or investigator noncompliance would be reportable to the FDA according to the regulations.

Mr. STUPAK. So did you report to the FDA? You had 83 violations alone just on Kirkman-Campbell. Did you report to the FDA?

Ms. PRICE. No. We had no obligation at that point to report any of those violations.

Mr. STUPAK. Why wouldn't you have an obligation, you're the IRB?

Ms. PRICE. We received that information 3 months after her site was closed out.

Mr. STUPAK. No, you received the memo that we talked about, memo number 33, it's Exhibit No. 33, the one from Ms. Cisneros to Ms. Wallace, you received that. Didn't you have a responsibility to report that to the FDA?

Ms. PRICE. It was human error that that didn't get elevated as it should have been.

Mr. STUPAK. Well, besides this one right here, you had 83 more complaints about Kirkman-Campbell. You didn't report those to the FDA?

Ms. PRICE. I want to clarify something, if you don't mind, on a former answer. We did not become aware of this telephone contact report until January 23, 2008, at which time you all were immediately notified.

Mr. STUPAK. Wait a minute. You testified earlier you became aware of an electronic format that was in the electronic files in 2006.

Ms. PRICE. As we reviewed our information, it did show up on our electronic report. However, we did not generate that report for Grassley's committee. It did not appear in our hard copy files. And we did not see that memo. No one opened that memo until January 23, 2008, one hour before you all received it.

Mr. STUPAK. OK. Well, then let's go over this again then. Kyle, do you have that exhibit? Let me show you a letter of February 27, 2007, from this Committee signed by Mr. Dingell and myself, addressed to you as executive officer and chairman of the Copernicus Group. Do you have that document, Kyle? I think your counsel has it right there. He's handing it to you. OK?

Ms. PRICE. Yes, sir.

Mr. STUPAK. We're asking for certain documents. It goes to page 2, top of the page, adverse events reported to Copernicus relating to the subjects in Study 3014 regardless of the source of these re-

ports. You indicated you knew it existed electronically in about 2006 at the request of Senator Grassley's request. Now you're telling me today you didn't realize that Exhibit 33 existed until 2008. So for almost a year you sat on it without giving us the information we requested, right?

Ms. PRICE. No one had opened the document. After we received this letter dated February 27, 2007, our counsel met with your staff and decided——

Mr. STUPAK. And your counsel or you did not tell us about this electronic file that you never opened, right?

Ms. PRICE. Excuse me?

Mr. STUPAK. You or your counsel never told us about the electronic file?

Ms. PRICE. We didn't know it existed. We only knew that after we investigated how this thing turned up now, because we thought that it was——

Mr. STUPAK. So you expect me to accept you knew the report was there in 2006, you saw it for Grassley when Senator Grassley asked, but you expect me to accept the fact that since you didn't open it you had no obligation to produce it to us?

Ms. PRICE. I think we had an obligation if we would have opened it, but we did not and I'm sorry for that.

Mr. STUPAK. So to get around a request you just don't open the file?

Ms. PRICE. Not intentionally.

Mr. STUPAK. I mean, the U.S. Senate asks, we ask, and then the day you manage—how is it you come to think about it the day before you're brought in before the committee?

Ms. PRICE. It was discovered the day before I was to meet with your subcommittee or your staff, sir.

Mr. STUPAK. Right. It was discovered earlier in 2006, but you just don't remember it until the day before you come to the committee. Isn't that a coincidence?

Ms. PRICE. After further investigation it did appear in an electronic search for Grassley, but it wasn't prepared for Grassley.

Mr. STUPAK. Then let's go back to what I was just asking you about. Are you responsible for reporting and you never reported anything to the FDA about these 83 reports or this report, Exhibit No. 33, from Ms. Cisneros, the telephone call to you? And you're responsible for reporting noncompliance to the FDA, correct, that is established, right?

Ms. PRICE. Yes, sir.

Mr. STUPAK. And all these reports you had, the 83, this one from Ms. Cisneros, you did not give that to the FDA, correct?

Ms. PRICE. Correct. It did not rise to the level of any anticipated problems at that point in our history in 2002.

Mr. STUPAK. That's your judgment?

Ms. PRICE. That was our policy and procedure at the time.

Mr. STUPAK. Well, you're familiar with 21 C.F.R. 56, the IRB functions and operations, right?

Ms. PRICE. Yes, sir.

Mr. STUPAK. Does it not say in that that any instance of serious or continuing noncompliance with these regulations or the require-

ments or the determinations of the IRB, are you not required to report that to the FDA in order to fulfill requirements—

Ms. PRICE. It does say that in words to that effect. I believe so.

Mr. STUPAK. OK. So you violate this policy, too?

Ms. PRICE. No sir, I don't believe we do. That's your opinion and I don't share that opinion.

Mr. STUPAK. So you don't feel you have to follow 21 C.F.R. 56, Section 108, subsection (b), IRB functions and operations?

Ms. PRICE. We do follow up 21 C.F.R. We received 83 memos to file 3 months after an investigator closed and we had no obligations.

Mr. STUPAK. Your responsibility doesn't stop when Ms. Kirkman stops the study; it continues.

Ms. PRICE. According to the regulations, we review investigators and have that authority through the time that we're overseeing them as IRB of record. Once they have a final status report they are closed.

Mr. STUPAK. Well, when is the final study status closed, when it's presented to the FDA?

Ms. PRICE. No, sir, when they close at our site—when they close the IRB.

Mr. STUPAK. So once the site closes you have no more responsibility to report problems with patient safety?

Ms. PRICE. We have no regulatory obligation, no.

Mr. STUPAK. How about legal obligation under 21 C.F.R. 56?

Ms. PRICE. Our interpretation of that regulation would not have indicated that we would have needed to provide those.

Mr. STUPAK. Well, that's your interpretation. How about moral obligation to the patients? If your IRB is there to protect patient safety, don't you have a moral responsibility if you have questions on patient safety to report it to the FDA or to Aventis or to the PPD?

Ms. PRICE. I started this company in 1996 and I have the utmost respect for the regulations and have run my business providing ethical review. And I do have obligations, according to our standard operating procedures, which we had in place at the time, and I felt that it met the requirements.

Mr. STUPAK. I'm not asking about standard operating procedures. I'm asking you if you have a moral obligation since you're responsible for patient safety when you see 83 reports just from one site to report that to somebody, like the FDA to Aventis or PPD?

Ms. PRICE. Aventis sent them to us and PPD sent them to us, so they were already aware of them.

Mr. STUPAK. OK. Well, how about do you have a moral obligation to the FDA?

Ms. PRICE. Not at the time, according to our standard operating procedures.

Mr. STUPAK. How about today, do you have a moral obligation to the FDA to report documents to them that refer to patient safety?

Ms. PRICE. If something came in similar to this today, number one, we revamped our standard operating procedures. And as I said, information about unanticipated problems is more clearly understood across the board for institutional review boards. I feel confident that anything that would come in today that would rise to

this level would be reported appropriately to the board and they would make a determination on what should be done, which would probably include notifying the FDA.

Mr. STUPAK. Did you have reports from other sites other than Kirkman-Campbell?

Ms. PRICE. What type of report, sir?

Mr. STUPAK. On patient safety issues, protocol violations.

Ms. PRICE. There were a number of memos to file. I would anticipate that there would have been others, yes.

Mr. STUPAK. So you don't know if there were others. Do you anticipate there were others?

Ms. PRICE. I know that there were memos to file. I don't know the specifics of the contents of those.

Mr. STUPAK. Well, did you report any of those violations to the FDA?

Ms. PRICE. No, sir. We weren't reviewing protocol deviations or memos to file at that point in 2002.

Mr. STUPAK. So all these things come in and it was your standard operating procedure not to report these violations to the FDA or anybody?

Ms. PRICE. That's right.

Mr. STUPAK. So what are you there for? Why do you exist?

Ms. PRICE. IRBs perform a very integral part of a role in—

Mr. STUPAK. I agree. I've done many hearings on IRBs. Their main focus is to protect patient safety. IRBs started in the university setting, in a public setting, but now they've gone to outside the private, for-profit groups like yourself. And if we don't hit the nail right on the head on standard operating procedures you just feel you have no responsibility for patient safety.

Ms. PRICE. I disagree. We work very closely within an ethical and regulatory framework as put out.

Mr. STUPAK. When I asked about the ethics you didn't have an answer. You just said that was in your standard operating procedures and under 21 C.F.R. You didn't think you had any legal responsibility. So where do the ethics come in now?

Ms. PRICE. We review everything. Our board reviews everything, according to the Belmont Report, the ethical principles in the Belmont Report, which talk about autonomy of individuals, which talks about risk benefit association and also it talks about distribution of justice.

Mr. STUPAK. The bottom line, you blew it here, right? You didn't do your job here, on this study, correct? Is that fair to say?

Ms. PRICE. We had a human error in not addressing this call from an investigative site monitor.

Mr. STUPAK. Not just a call, but the 83 other violations and the other violations from other sites are reported to you, you had a responsibility to tell the FDA and you didn't say anything to the FDA on any of them?

Ms. PRICE. I'm sitting here today telling you that I think we did a good job for what we did at the time.

Mr. STUPAK. Good job of saying nothing to the people who need to know, which was the FDA, right? I don't mean to be argumentative but this is ridiculous. Mr. Chairman, you had a couple questions on IRBs you want to ask?

Mr. DINGELL. Mr. Chairman, I think you're raising more questions than we're getting answers to. The witness here that you've been just inquiring of, what is the name of your firm, ma'am, if you please?

Ms. PRICE. Copernicus Group IRB.

Mr. DINGELL. What is your relationship to that company?

Ms. PRICE. I'm the founder and CEO.

Mr. DINGELL. How many employees do you have?

Ms. PRICE. We currently have about 70 employees.

Mr. DINGELL. What is the net worth of the company?

Ms. PRICE. Net worth meaning?

Mr. DINGELL. What's the net worth?

Ms. PRICE. I would say in the millions of dollars.

Mr. DINGELL. Now, tell me, how long has the company been in existence?

Ms. PRICE. I started the company in 1996.

Mr. DINGELL. Are you a publicly held company?

Ms. PRICE. No, sir, privately held.

Mr. DINGELL. Privately owned?

Ms. PRICE. Yes.

Mr. DINGELL. Do you file annual reports with anybody?

Ms. PRICE. We file taxes.

Mr. DINGELL. Taxes, that's all?

Ms. PRICE. And annual corporate reports.

Mr. DINGELL. You don't file any reports to the SEC or any of the State regulatory agencies?

Ms. PRICE. No, sir.

Mr. DINGELL. What was your earnings last year?

Ms. PRICE. Earnings last year? Revenue top line was about \$13 million.

Mr. DINGELL. And from where did you earn that \$13 million?

Ms. PRICE. A number of clients.

Mr. DINGELL. From what?

Ms. PRICE. A number of clients and sponsor organizations that submitted studies to us.

Mr. DINGELL. You earned it then functioning as an IRB?

Ms. PRICE. Yes, sir. That's the basic function of the company.

Mr. DINGELL. Did you earn money from any other source?

Ms. PRICE. No, sir.

Mr. DINGELL. Now, how are you retained to do this work? Are you retained by the companies that have these matters before Food and Drug or does Food and Drug appoint you or how are you appointed?

Ms. PRICE. In the case of Kirkman-Campbell or in the case of 3014 we were contacted by the CRO. We are usually paid by the sponsor companies, and that would be like the pharmaceutical sponsors.

Mr. DINGELL. So you're paid by the sponsor company, but by whom are you selected?

Ms. PRICE. The pharmaceutical company or their designee, which would be sometimes CROs select us, or investigators sometimes approach us to serve as an IRB of record for their studies.

Mr. DINGELL. How many companies do you work for? Could you submit us a list of the companies for whom you have worked?

Ms. PRICE. Yes.

Mr. DINGELL. And could you submit us also a list of the companies to whom you have provided or rather—by whom you have been paid and for what, to what, let's see, for what, for inquiries in what matters were you paid by what companies over the period since this matter of Ketek? And starting with Ketek and those matters and the years in which you worked on that going forward, what companies—would you submit to us what companies you have worked for as an IRB?

Ms. PRICE. Certainly. You're asking for a list of studies we have reviewed since 2001?

Mr. DINGELL. Yes. I want it going back to the year on which you worked with or for Ketek, the companies.

Ms. PRICE. Yes, I can do that.

[The information was not submitted for inclusion in the record.]

Mr. DINGELL. And how much you were paid on each. And on which matters and on which pharmaceuticals you served as an IRB. Now, is your company a for-profit or nonprofit company?

Ms. PRICE. A for-profit.

Mr. DINGELL. For-profit. And I believe you told me that all you do is function as an IRB, is that correct?

Ms. PRICE. Our basic function is to provide ethical review for clinical research.

Mr. DINGELL. Now, what does this involve? What do you do here when you do this?

Ms. PRICE. Institutional review boards will receive information. Are you familiar with protocols? Protocols are actually submitted by the sponsor company. We're usually—protocols and informed consent documents are submitted by the sponsor companies. We have our board members, who are a group of diverse individuals with scientific and nonscientific backgrounds, who review the informed consent documents as well as the protocols. And based on the ethical framework of the Belmont Report and the clinical regulations we decide whether there is more risk than—more benefit than risk to doing the studies and conducting the research. We then take a look at the informed consent document. And we determine whether that information is sufficient for an investigator to use to do the informed consent process. The document includes certain things as listed in the regulations, certain elements, letting a subject know that they can voluntarily be in the study and come out, back and forth, at any time, risk benefits and that sort of thing.

Mr. DINGELL. Now, tell us, do you review testimony or review documents that are submitted by the company in connection with the questions before Food and Drug? Do you review the competence or the qualifications of the persons who are doing the research or presenting papers or testimony?

Ms. PRICE. Yes. Per the regulations, the investigators are selected by the sponsor company. And part of our review is to look at the submission packet for the investigators. And in the case of Study 3014 we did spot checks of licensure.

Mr. DINGELL. I'm trying to understand here with more than a little difficulty exactly what you do.

Ms. PRICE. I think that institutional review boards have always had difficulty explaining what they do. I wish I could explain it better. We review clinical research from an ethical perspective. We are not on the ground monitoring at the investigator site. We try to assure the subject safety through ethical review.

Mr. DINGELL. You do an ethical review?

Ms. PRICE. Yes, sir, of the protocol, the informed consent document.

Mr. DINGELL. What is an ethical review? What constitutes an ethical review?

Ms. PRICE. We base our ethical review on the Belmont Report, the issues released in the Belmont Report. And those are ethical principles that reflect the conduct of good clinical research. As I stated before, that has to do with autonomy of subjects, making sure that there is an informed consent process that takes place. We look at the research or the IRB will look at the research and determine if there is enough benefit to do the study, if something, generalizable knowledge can come out of it. And thirdly, we look at justice. Is there—is there one group that is receiving most of the burden of research or is it equitable across the board. In addition, our IRB will look and see that there is a monitoring plan in place, that there is going to be some type of monitoring for the study. Then ongoing investigators are obligated per the regulations to submit—

Mr. DINGELL. Does your work require you or permit you to look to see whether the data is true, factual and correct?

Ms. PRICE. No, sir, we don't deal with data.

Mr. DINGELL. Now, how do you make an ethical review without knowing whether or not the information received is true, factual and correct?

Ms. PRICE. That is not our role.

Mr. DINGELL. That's not your role.

Ms. PRICE. No, sir.

Mr. DINGELL. Do you look to see whether the proper information has been submitted to support the allegations and the statements made either by Food and Drug or by the applicant?

Ms. PRICE. No, sir. That's a monitoring function that's the responsibility of the sponsor.

Mr. DINGELL. Do you look for whether false statements are made in connection with the application or whether the studies that are submitted are in fact valid, truthful, factual, correctly and honestly done?

Ms. PRICE. No, sir, we don't per se.

Mr. DINGELL. Do you do that?

Ms. PRICE. We rely on the investigators to communicate with us. And in this case sponsors.

Mr. DINGELL. So then do you know whether the studies that are submitted as a part of your ethical evaluation are factual, truthful, correctly done?

Ms. PRICE. We don't have a role after the study is completed to follow up on the analysis of the data or the submission to the FDA.

Mr. DINGELL. Now, you got \$375,000 for this matter, I believe, is that right?

Ms. PRICE. Yes, sir. That was how much we made off the study.

Mr. DINGELL. Exactly what did you do for this \$375,000?

Ms. PRICE. We reviewed the protocol, the informed consent document.

Mr. DINGELL. You reviewed what?

Ms. PRICE. We reviewed the protocol, the informed consent document, we reviewed investigator packets and we looked at serious adverse events as they came in. We fashioned an informed consent document that was to be used by investigators for the informed consent process.

Mr. DINGELL. Did you ever go into the question of whether or not the studies were factual or adequate?

Ms. PRICE. That determination was made—I'm a little unclear on your factual comment. But certainly the assessment of the institutional review board members themselves would have gone into whether they felt the study was designed in an appropriate way and would—

Mr. DINGELL. Did you ever interview anybody about the studies as to whether they were factual or correctly done or included all the persons that should have been interviewed or whether or not all the persons upon whom the tests were supposed to have been performed were either properly treated or in fact existed or had had the results that would indicate a proper study?

Ms. PRICE. No, sir, we didn't interview anyone.

Mr. DINGELL. Did the Ketek study comply with the Belmont review?

Ms. PRICE. In the opinion of the institutional review board, yes, it met the requirements, yes, sir.

Mr. DINGELL. It did.

Ms. PRICE. Yes, sir.

Mr. DINGELL. Why do you say that?

Ms. PRICE. Our board is trained to look for certain things. And they use the Belmont Report for their guidance, and then the regulations. And our preliminary review is initially to review the protocol and informed consent document.

Mr. DINGELL. Now, could you pass the Belmont review and still have fraud?

Ms. PRICE. A study could certainly be approved. And it was in this case. The study was approved on the Belmont principles; however, there was fraud by an investigator or investigators in the study.

Mr. DINGELL. So you couldn't ask the Belmont review if there was fraud there, is that right?

Ms. PRICE. Yes.

Mr. DINGELL. Can you make the bold statement that there was no fraud in connection with Ketek or any of the studies that were made with regard to the approval of their applications by Food and Drug?

Ms. PRICE. Can I make the statement that there was no fraud? I think that it has been found that there was fraud.

Mr. DINGELL. Say that again.

Ms. PRICE. There has been found that there was fraud.

Mr. DINGELL. There was fraud.

Ms. PRICE. According to the Food and Drug Administration, yes.

Mr. DINGELL. I'm sorry.

Ms. PRICE. According to the Food and Drug Administration. That was not our assessment. That was the assessment of the FDA.

Mr. DINGELL. So you don't know whether there was fraud or not or you do know there was fraud?

Ms. PRICE. According to the FDA there was fraud, so I would say yes, there was fraud.

Mr. DINGELL. And your ethical review did not reveal that there was fraud here?

Ms. PRICE. No, sir, it did not.

Mr. DINGELL. I find that a curious ethical review. Mr. Chairman, I thank you.

Mr. STUPAK. Thank you, Mr. Chairman. Mr. Barton for questions. We've been going around more than once for this panel since we're only on Ms. Price, it seems like.

Mr. BARTON. Thank you, Mr. Chairman. I apologize. I've been stuck in airports most of the day. My plane was delayed, so I've not been able to attend the entire hearing. My questions are going to be for Dr. Eshelman. It's my understanding, Doctor, that the Aventis PPD contract for this Study 3014, that Aventis was responsible for bringing the investigators into compliance; if that wasn't possible, terminating their participation in the study. Is that your understanding?

Mr. ESHELMAN. PPD was not responsible for the termination of an investigator, if I understood your question.

Mr. BARTON. Well, the question is the staff has informed me that Aventis was responsible for bringing investigators into compliance, but if they couldn't do it, then Aventis had to terminate their participation into the study?

Mr. ESHELMAN. That's correct, sir.

Mr. BARTON. Did the contract specify which party should notify FDA in the event that it did discover fraud?

Mr. ESHELMAN. I think that the regulatory communication function was retained by Aventis under the terms of the contract.

Mr. BARTON. Did anything in the contract prevent your company, PPD, from notifying FDA about your concerns?

Mr. ESHELMAN. I guess only under the terms of confidentiality as they might or might not have applied. I mean there was certainly nothing explicit or implied by Aventis or anyone else that would have otherwise prevented us from contacting a regulatory body with the exception of the particular retention by Aventis of regulatory communication in this instance, which is a long-winded way of saying all that stuff notwithstanding we could still do whatever we wanted to.

Mr. BARTON. In other studies that PPD has been involved with with the FDA, has your company ever notified the FDA about fraud when it wasn't directed to do so by the particular drug sponsor?

Mr. ESHELMAN. I can't say with assurance because I don't have the facts in front of me. But on occasion PPD is assigned all of the responsibilities for a particular study, including communication with regulatory bodies. And in such an instance if there were reason for disqualification of an investigator we certainly would communicate that with FDA and other appropriate bodies. I don't know whether we have specifically done that or not. I certainly know

that in the course of our work over the years we have made recommendations to sponsors on a large number of issues. And sometimes they are followed through and sometimes they're not because sometimes there is a bona fide difference of opinion on a site.

Mr. BARTON. Please describe your company's role in vetting physicians for participation as clinical investigators. Do you rely on the FDA debarment and disqualification list as part of your vetting?

Mr. ESHELMAN. Yes, sir. And we screen investigators against that list all of the time. And it's typical that when we contract with a company like Sanofi-Aventis we warrant that in fact we have done that. When we sign up investigators, also we try to qualify them on a basis of their training and experience. We also request a copy of the medical license that is valid at that time.

Mr. BARTON. Do you conduct any other research to determine whether the physician has been convicted of a felony relating to a drug product?

Mr. ESHELMAN. My assumption is that if a physician has been convicted of a felony, their license would be revoked. Now, I'm not a lawyer, I don't know if that's true. That's my assumption.

Mr. BARTON. Well, I mean the basic question is do you do any outside independent research or do you rely strictly on the list that the FDA provides in terms of debarment and disqualification?

Mr. ESHELMAN. No, sir. We get a copy of their current medical license. I'm also informed that post, I think 2004, we became aware of certain Web sites that we could go to, which would indicate whether or not there had been sanctions by medical licensure boards against particular physicians. So we can also go to those in most States. I believe that maybe this is not true in Wisconsin, but in most States it is.

Mr. BARTON. I'm a little bit confused. Is all you basically do, you do a status check on the license that the physician under review for participation, that that license is current, is that the extent of your investigation?

Mr. ESHELMAN. No, sir. We also look at their curriculum vitae to be sure that they are in fact trained appropriately for what they are supposed to do.

Mr. BARTON. Do you believe that the debarment and disqualification lists that the FDA provides accurately reflect the number of individuals who have been convicted of crimes relating to drug products?

Mr. ESHELMAN. Based on the testimony that I've heard today with particular reference to Dr. Kirkman-Campbell, I guess I would have to say no.

Mr. BARTON. Well, we're releasing a report today, if we haven't already, that shows that the FDA has been hardly stalwart in pursuing debarment even when the factual and legislative predicates are met. Even when they're mandated do they seem to drag their feet. So if we rely on these debarment and disqualification lists as provided by the FDA, there are going to be lots of doctors out there and lots of folks that probably shouldn't be allowed to participate. And that's a personal opinion of mine. That's not necessarily an opinion of the committee.

If what I just said is true, how does that impact your ability to screen clinical investigators?

Mr. ESHELMAN. Well, you know, if the debarment process is flawed—

Mr. BARTON. Well, it's almost nonexistent.

Mr. ESHELMAN. Well, that could present some serious issues for us obviously and also sponsors. I'm not sure how that would go to our contracts because they, in most cases, do rely on screening against this debarment list. But it's a serious issue.

Mr. BARTON. My last question, Mr. Chairman. In a conference call with Aventis in March of 2002, PPD discussed the problems it had identified at Dr. Kirkman-Campbell's site. According to the minutes of that phone call found at tab 5, Aventis tried to take certain steps to identify whether the fraud had occurred. At the time of this call, Dr. Eshelman, did you agree with Aventis' response as to how it could address or how it would address the fraud concerns?

Mr. ESHELMAN. I was not aware of the details of that at that time.

Mr. BARTON. OK. So you had no reason at that time to dispute one way or the other Aventis' concerns?

Mr. ESHELMAN. No, sir.

Mr. BARTON. Thank you.

Mr. STUPAK. No further questions from the ranking member.

Mr. Markey, a member of the full committee, is here and would like to ask some questions of this panel. With unanimous consent, I recognize Mr. Markey for 5 minutes for questions. Mr. Markey, please.

Mr. MARKEY. Thank you, Mr. Chairman, very much. Ms. Price, after everything that you've experienced, what reforms has Copernicus put in place to make sure this does not happen again?

Ms. PRICE. Thank you for that question. I've tried to make it clear that we have, we've always looked at ways that we can improve our process.

Mr. MARKEY. How have you improved it?

Ms. PRICE. We have redone our—or our standard operating procedures have evolved immensely over the past 6 years. We participated in a voluntary accreditation program.

Mr. MARKEY. Do we need mandatory policies that are on the books in terms of how Copernicus and companies like Copernicus operate? Should we put mandatory controls on the books that are explicit?

Ms. PRICE. Mandatory controls? The regulations are already in place about institutional review boards. I think it would be difficult. Are you asking if there should be mandatory standard operating procedures?

Mr. MARKEY. To avoid problems in the future should we go back and write in specific rules, regulations and laws to make sure that there are tighter safeguards in the future?

Ms. PRICE. I'm not sure how to answer that because I think that the regulations are in place and they leave some interpretation. It's definitely open for interpretation. FDA and OHRP are certainly trying to—

Mr. MARKEY. So you're saying that the regulations in your opinion just aren't explicit enough and that they have to be rewritten in order to be clear that you are violating a policy, a law, if you

act in a way that is inconsistent with those regulations? So you think we should go back again and rewrite those regulations, is that what you're saying?

Ms. PRICE. I think that there needs to be some looking at the regulations. But no, I'm not saying that we need to rewrite the regulations.

Mr. MARKEY. OK. I wish that you were saying that, but it would be helpful to us that you admitted that there were serious problems that existed.

Dr. Chew, it is well established that at some point during the completion of Study 3014 all of you knew that there were breaches in the study protocol. Dr. Chew, did Aventis contact the FDA?

Dr. CHEW. In the case of Dr. Kirkman-Campbell, no. But in the case of two other investigators, yes.

Mr. MARKEY. Now, Dr. Eshelman, did PPD contact the FDA?

Mr. ESHELMAN. No, sir, we did not.

Mr. MARKEY. You did not. And why not?

Mr. ESHELMAN. Well, first of all, it was a contractual obligation reserved by Sanofi-Aventis. Secondly, there was some disagreement between the two firms as to whether or not the events at Dr. Kirkman-Campbell's site rose to the level of fraud or if they were just GCP violations.

Mr. MARKEY. Dr. Chew, when did Aventis first become aware of the anomalies associated with the study?

Dr. CHEW. From my review of the record, Congressman, on January 17th or 18th of 2002 an Aventis audit was done. And at that time with 327 sites having been randomized, and all informed consents being reviewed, there were issues then raised of dating of the consent forms by staff when the informed consent expressly states that the dating must be done by the patient. And there were other irregularities in the informed consent. There were also issues raised at that time of randomization clusters that needed to be evaluated, as well as documentation errors, as well as questions about the blood sample.

Mr. MARKEY. And what did you do to address these anomalies at that time, in January 17th?

Dr. CHEW. Well, at that time there was a request for additional data. Because at that time the number of actual cases that were reviewed, because of the volume of the randomization, the number of cases, individual patient records actually reviewed was 10. And I believe on November 29 of 2001, three by PPD. So clearly there needed to be more in-depth information obtained. And that was obtained by PPD on their 3-day monitoring on February 18th, 19th and the 21st, and that culminated in the teleconference on March the 4th to evaluate the potential for scientific misconduct and fraud.

Mr. MARKEY. Now, on June 19, 2002, Ms. Jean Noon from PPD e-mailed Ms. Nadine Grethe of Aventis informing her we are still getting conflicting information from site S. They will tell us one thing, then the next time we call they tell us the opposite. This is particularly problematic when it comes to whether a subject was ever consented or not and what effect the drug subject took. Ms. Noon then continued the e-mail with specific examples of multiple treatment and informed consent problems. To this e-mail Ms.

Grethe replied, quote, at this point it is too late to change anything in the database. They filled it out with an informed consent date. And this is what we are going with. We are not changing this again. They screwed up. They will now have to take the blame. Also, if they keep changing their minds, then I really do not believe them now.

Dr. Chew, what should Ms. Grethe have done in response to this e-mail?

Dr. CHEW. Congressman, I saw that e-mail. It was difficult to know specifically which sites and which patients were discussed. With hindsight of course I think that more information could have been found out. I'm just inferring now that there probably were differences in documentation and inconsistencies in correspondence. And it's my inference that they, the team, went with the best documentation they had.

Mr. MARKEY. Is she still with Aventis?

Dr. CHEW. Ms. Nadine Grethe is no longer with Aventis.

Mr. MARKEY. And why did her separation occur?

Dr. CHEW. I'm not quite clear, but I believe it was for other professional opportunities, to my knowledge.

Mr. MARKEY. What has Aventis done to make sure that these kinds of errors do not recur in conjunction with future studies?

Dr. CHEW. There has been a tremendous effort in looking at the lessons of 3014. Investigator selection, investigator training, investigator retraining, especially if they're naive. One of the issues of this trial is it enrolled so fast. It was 24,000 patients in 3 months, one winter season, to catch the infections. This was reviewed with FDA. One winter season was felt to be adequate. One of the issues with such a large trial when it is recruiting so fast is the monitoring of these sites has to be on top of the situation. And when you look at the monitoring plan, which was designed for a typical controlled clinical trial, not a real world study, immediately I saw that there was a disconnect. Most of the patients had been randomized in the 3-month period before the monitoring could get on top of it. So one of the things we've done now is to control the rate of enrollment and put a cap on the enrollment. And you don't go above that cap until you've been validated that you have good quality data that has been looked at internally.

So the quality has to keep up with the quantity. That's one of the key things. You see in this trial there was not a cap. There was a recommendation. Now there's a cap. And so that we go lockstep, quantity and quality. So that's one of the big things. Training, new SOPs and just a heightened awareness. Fraud is a very uncommon issue.

Mr. MARKEY. Well, in light of your experience could this sort of situation happen again?

Dr. CHEW. I will never say never, but I will say we will take all that's humanly possible to minimize the chance of this happening again. I think fraud—we heard this morning fraud is something that does occur. But we're going to minimize the scope, the scope, of this. And also not only fraud, but its serious GCP noncompliance. That's not fraud, but that's enough, that's enough, in retrospect that I wished Aventis had called FDA to share their concerns and some more clarity on the threshold, and it may be difficult, the

threshold of contacting to not be burdensome to the agency, but to be responsive to problems. That's an area that I think the industry would appreciate some guidance on.

Mr. MARKEY. Well, I think you're going to get all the guidance you need going forward, and this committee will provide that guidance for you and for other companies that will perhaps be in doubt as to what their responsibility is once potential fraud is identified to disclose it in a reasonable fashion so that the public health is protected. And I thank you, Mr. Chairman, for allowing me to participate.

Mr. STUPAK. Thank you, Mr. Markey. Dr. Chew, let me ask you this. Do you think PPD did a good job for Aventis?

Dr. CHEW. Looking back, I think PPD did a good job for Aventis.

Mr. STUPAK. How about Copernicus, did they do a good job for Aventis?

Dr. CHEW. It would be harder for me to say because the documentation of the exchange between Copernicus and Aventis at that time was not—I didn't see an awful lot of documentation.

Mr. STUPAK. Should Copernicus have let you know about the 89 or 83 complaints they had?

Dr. CHEW. Well, the memos to file, they came from Aventis. In other words, Aventis notified them.

Mr. STUPAK. So you knew about it?

Dr. CHEW. Those memos to file were sent to them.

Mr. STUPAK. Did you expect the IRB, Copernicus here, then to notify the FDA?

Dr. CHEW. Well, in hindsight I—looking back, I mean I would have expected Copernicus not to have, because it was the feeling when I—

Mr. STUPAK. Who does Copernicus work for, the patients or for you?

Dr. CHEW. The patient's safety is the IRB responsibility. So the ultimate responsibility, as it is with the sponsor, is patient safety.

Mr. STUPAK. OK. The 24,000 people you've enrolled in this Ketek study, have you contacted them and said there may have been some problems with this study to see how they're doing, because you have liver toxicity, you have an eye problem associated, you also have I think toxicity around the heart, right? Didn't you have a cardiac toxicity here, too; three toxicities, eye, liver and heart, right?

Dr. CHEW. Again, in this trial—

Mr. STUPAK. Did you contact the patients?

Dr. CHEW. The patients were not contacted beyond the trial because half the trial was another drug for which you could compare.

Mr. STUPAK. OK. Well, how about the 12,000 then on Ketek, did you contact them?

Dr. CHEW. The 12,000 patients were filed before the trial, but they were not contacted to my knowledge after the trial was over, unless they had an ongoing adverse event.

Mr. STUPAK. OK. How do you know if they're having an ongoing adverse event if you don't contact them?

Dr. CHEW. The study protocol had a 5- or 10-day treatment, but then there was a 35-day or 27- to 35-day follow-up well beyond the existence of the drug in the body.

Mr. STUPAK. How many of the people, 12,000 people, who were supposed to receive Ketek, how many actually received it?

Dr. CHEW. The details I would have to get back to you on.

[The information was not submitted for inclusion in the record.]

Mr. STUPAK. Give me an estimation, how many actually received it?

Dr. CHEW. I'm guessing that those who were assigned more than, I'm just guessing, but that there would be 90 percent or more.

Mr. STUPAK. How many of Dr. Kirkman's patients, the 407 she had enrolled in her study, how many of them actually received Ketek, do you know?

Dr. CHEW. I don't know, and that's because we didn't talk to the patients. Aventis at that time did not speak with the patients to see if they actually had received the drug.

Mr. STUPAK. OK. Go to the binder book. Ms. Price, if you could hand that down. Mr. Markey read parts of Exhibit No. 21 to you. That was the memo there from Nadine Grethe, who you said is no longer with Aventis. At this point it is too late to change anything databased. They filled it out with an informed consent date and that is what we're going with. We are not changing this again. They screwed up. They will have to take blame. And also if they keep changing their minds then they really do not believe them now.

You followed up, Aventis followed up with this e-mail, right? This was in June of 2002. You followed up with an audit, did you not, in Ketek and in your different sites?

Dr. CHEW. I think the audits, I believe, went through this period. I have to get the precise date in which they stopped, but I think they did go through this period.

[The information was not submitted for inclusion in the record.]

Mr. STUPAK. OK. So after this e-mail you went through to do an audit to see what was going on with Ketek, right, with this study?

Dr. CHEW. There may have been—this I think would have been near the end of the monitoring period. By monitoring versus auditing, I mean monitoring would be the PPD function. You would have to kind of get the actual dates.

Mr. STUPAK. Let's go to Exhibit No. 26 right there in front of you. Now, this is an audit by Aventis auditors, is it not?

Dr. CHEW. Yes. It appears to be, yes.

Mr. STUPAK. And the date of the original message is Tuesday, October 29, 2002, correct?

Dr. CHEW. That's right.

Mr. STUPAK. So this is about 3 or 4 months after Exhibit No. 21, right, when you're concerned about it?

Dr. CHEW. That's right.

Mr. STUPAK. And what you did, you did an audit of the sites that had enrolled more than 100 subjects in this Ketek Study 3014, correct?

Dr. CHEW. In this listing, yes.

Mr. STUPAK. In every one of them, if you turn to the next page starting with Dr. Gardner, Dr. Anne Kirkman-Campbell, Dr. Lang, Dr. Shoemaker, Dr. Price, Dr. Tenscal, Dr. Stone, Dr. Blanchard, Dr. Glice, Dr. Resnick, they all had significant problems as to the

review of your own auditor, Aventis auditor, significant problems, correct?

Dr. CHEW. Yes.

Mr. STUPAK. And not just the informed consent, but significant problems that required corrective action this auditor said, right?

Dr. CHEW. Yes, corrective action.

Mr. STUPAK. Right. It said in every one of them significant issues that require corrective action. What corrective action did Aventis take?

Dr. CHEW. Without commenting specifically on each site and each intervention, I believe that at the time you can see where the audit dates were. The audit dates were January, February and March. The enrollment had completed. The monitoring at the time and the auditing at that time was to document what was found.

Mr. STUPAK. Significant problems were found.

Dr. CHEW. What was found. And that the investigator was aware of this and documented it. These were monitoring visits that occurred. Normally monitoring visits are to help future patients, not only to fix the problem you have now, but for future patients. To my knowledge, probably most of the patients had already come and gone.

Mr. STUPAK. Sure. But let's get to the basis here.

Dr. CHEW. Yes.

Mr. STUPAK. Based on 21 you had a problem. In June of 2001 you knew there was a problem based upon Exhibit No. 21, that there was serious problems here with your study. And you want to use this study to verify the safety of Ketek, Aventis does, right, that's the reason for this study?

Dr. CHEW. The request was to get additional safety information.

Mr. STUPAK. Right. So you do this large study. You say you have to do it during the flu season so you enroll 24,000 people. You use these sites all around the country, 1,800 sites.

Dr. CHEW. That's right.

Mr. STUPAK. And you audit 10 sites, right? Usually you do 10 percent of your sites, do you not? Isn't that the general standard?

Dr. CHEW. I don't know what the algorithm is, but it's more than 10.

Mr. STUPAK. Right. It should have been about 180 sites, but you only did 10. Aventis went through and audited 10 sites, the largest sites, correct?

Dr. CHEW. Well, I don't agree that it would have been 180, but it would have been more than 10. They should have done more than 10, in my view.

Mr. STUPAK. The point is you only audited 10 sites, 10 of the sites with the most patients in, correct?

Dr. CHEW. They were the high enrolling sites, yeah.

Mr. STUPAK. Correct, the high enrolling sites. So you did 10. You didn't audit any other sites, they did just 19, right?

Dr. CHEW. The monitoring was done of course more extensively, but the audit was on 10.

Mr. STUPAK. Only 10 sites. Those 10 sites with the high enrollment patients, right, high enrollment patients in these sites, these are ones you audited. And this is October 29, 2002, your auditor at every one of the sites, not just Kirkman-Campbell, but every one

of the sites finds significant problems in which corrective action has to be taken, correct?

Dr. CHEW. There were issues found that needed corrective action, correct. I think there are varying degrees of intensity.

Mr. STUPAK. Go through if you want. Every one of them says significant issues where corrective action is required. Every one of them. Significant GCP issues identified during the monitoring. They find in the audit significant issues requiring corrective action. Dr. Lang, significant issues that require corrective action. Dr. Shoemaker, a significant issue that required corrective action.

Dr. CHEW. I agree.

Mr. STUPAK. So the whole basis of your safety study in your audit showed that you had significant issues that required corrective action, correct?

Dr. CHEW. These were 10 sites that were audited.

Mr. STUPAK. These are the only 10 you did, right? In fact you could ask the question, all the sites you monitored you found significant issues that required corrective action, isn't that right?

Dr. CHEW. Not all the sites monitored had significant GCPs that required action.

Mr. STUPAK. Well, you just said that you only did 10 sites.

Dr. CHEW. I'm talking about the monitoring.

Mr. STUPAK. I'm not talking about the monitoring. Don't confuse this here. We're talking about the audit.

Dr. CHEW. Of the audits, yes.

Mr. STUPAK. Aventis only audited 10 sites in this big study and every one of them had significant issues that required corrective action, correct?

Dr. CHEW. They had significant GCP issues that required corrective action, that's correct.

Mr. STUPAK. So how in good conscience could Aventis submit the study when every one of the audit sites there were significant problems to the FDA to show the safety of Ketek?

Dr. CHEW. My answer to that, Congressman, is that to my knowledge these actions were not ignored, they were discovered and they were corrected and documented. Not all of them affect—to my knowledge, not all of them bore on the safety issue of Ketek.

Mr. STUPAK. Well, really? Significant issues that require corrective action? The study is over. You only had this window, the flu season, as you said, to get it done. You can't go back and replace that flu season, it's over. You audited. You find the basis during this limited period of time you had have significant issues at every site. And that's with the basis of the whole study. In every one of them you find significant—you didn't find any clean ones. Every one of them were wrong. But yet you present that study to the FDA for safety of Ketek. How could you do that? Why would you do that?

Dr. CHEW. It's my belief that these problems were identified and documented by the audit and subsequently corrected and documented.

Mr. STUPAK. How can you correct it? The flu season is done, the Ketek is over, you said they didn't have any more time. Ketek is over. These patients aren't getting it any more. And these are the

only patients you relied upon for the safety of the study that present to the FDA. How can you correct it?

Dr. CHEW. The issues were documented and corrective action was taken in terms of documentation. You're right, the patients had come and gone.

Mr. STUPAK. Yeah. How do you document blood splitting?

Dr. CHEW. I'm sorry?

Mr. STUPAK. How do you correct blood splitting? You get blood, you attribute it to different patients, even though it's not their blood to show that everything was fine for the safety of Ketek. How do you correct that?

Dr. CHEW. To my knowledge there was no—in these cases there was no evidence of blood splitting.

Mr. STUPAK. Dr. Kirkman-Campbell had blood splitting.

Dr. CHEW. But Dr. Kirkman-Campbell had the suspicion of blood splitting. Both PPD and Aventis did statistical analyses that were not conclusive, that were not conclusive in terms of the blood splitting, to my knowledge.

Mr. STUPAK. Ms. Price, did Copernicus check Dr. Kirkman-Campbell about blood splitting?

Ms. PRICE. No, sir.

Mr. STUPAK. No, you didn't, did you?

Ms. PRICE. Excuse me?

Mr. STUPAK. Blood splitting where you use blood from different—you didn't check that, did you?

Ms. PRICE. No sir, that's not our role.

Mr. STUPAK. How about you, Dr. Eshelman? Did the PPD check for blood splitting?

Mr. ESHELMAN. I believe that we turned up the suspicion of blood splitting.

Mr. STUPAK. Did you go back and check it to verify it to make sure it didn't have any effect—

Mr. ESHELMAN. Dr. Reynolds reviewed all of these cases, and I believe that Dr. Reynolds talked to someone at Aventis. I can't swear to that, but I believe that is true. I do know that the issue of the possibility of blood splitting was discussed between the two companies. And I think, as I said in my prepared remarks, this was evaluated statistically and otherwise by Aventis at the time. And their investigation did not seem to indicate mathematically that there was a type of variability that would be associated with blood splitting. Dr. Reynolds looked at it some more after that. Whether or not he did a mathematical analysis I cannot remember frankly.

Mr. STUPAK. So they didn't do the blood splitting, they didn't check it, so Aventis checked it and that was OK?

Dr. CHEW. There is I believe an e-mail from PPD indicating they did analyze for blood splitting looking at the delta and comparing of other sites. As with the Aventis analysis there was a suspicion but no firm proof, to my knowledge, of blood splitting.

Mr. STUPAK. OK. Let me ask you this. You hired Dr. Kirkman-Campbell, right, Aventis?

Dr. CHEW. To my knowledge, the investigator selection was the responsibility of PPD.

Mr. STUPAK. Dr. Eshelman, did you hire Kirkman-Campbell then?

Mr. ESHELMAN. The answer to your question is I don't know. My recollection is that the——

Mr. STUPAK. I love it. The main person and no one knows who hired her. It's amazing.

Mr. ESHELMAN. If you would let me finish.

Mr. STUPAK. Yeah, sure. I'm trying to, but my disbelief is just overwhelming me. Go ahead.

Mr. ESHELMAN. My recollection is that the identification and selection of investigators was a shared responsibility between Aventis and PPD. In other words, I believe that they had some investigator list. I believe that we had some investigator list. And that those were merged. And then subsequently the ones that came out of that as qualified were selected. So in the particular case of Kirkman-Campbell I can't tell you where that name came from, I'm sorry.

Mr. STUPAK. OK. PPD was hired by Aventis to monitor Study 3014 and detect noncompliance, isn't that correct, Mr. Chew?

Dr. CHEW. They were hired to monitor the study and of course to transmit to Aventis the findings.

Mr. STUPAK. Several of the PPD personnel involved in Study 3014 informed the committee staff that they were reasonably sure that Kirkman-Campbell submitted fraudulent data to Aventis. Did PPD then have a duty to notify the FDA; in your estimation, did PPD have a duty to notify the FDA when they reached this conclusion?

Dr. CHEW. I just have a personal opinion on that, because I don't know if there is a legal requirement. I believe anybody, anyone at any time if they suspect a problem, should feel free to notify FDA. I don't know if there is a legal answer to that. That would be my personal opinion.

Mr. STUPAK. Dr. Eshelman sort of indicated that there is a contractual obligation that they could not do that. You disagree with that or——

Dr. CHEW. Well, I think that by contract there are usually—assignment who does what. But in most cases if there is a problem, you agree on who does what and you do it. That is the way I would do it.

Mr. STUPAK. So did you require that—did Aventis require PPD not to report any problems?

Dr. CHEW. I am not quite sure, but I think it is my recollection that Aventis had the regulatory liaison contact. Just to keep things clear, who was doing what.

Mr. STUPAK. But as far as Aventis was concerned, Copernicus could notify the FDA, PPD could notify the FDA——

Dr. CHEW. Again, I am speaking individually. If there were an issue, I think what would happen—I am just hypothetically—is that Copernicus or PPD would discuss this, and there would be a resolution as to who does what. That has been my experience that usually there is consensus.

Mr. STUPAK. How about Aventis? Did you ever notify the FDA that you had trouble with this Study 3014? Did you ever sit down——

Dr. CHEW. Yes, we did. Yes, we did.

Mr. STUPAK. When was that?

Dr. CHEW. I believe in June of 2002, I believe, prior to the filing, when there were two sites who persistently refused to cooperate.

Mr. STUPAK. June of 2002. But tab number 26 shows that's October of 2002. So after—how about October, after your audit of October of 2002, did you notify the FDA of problems with the sites?

Dr. CHEW. To my knowledge, the two that were notified did not cooperate. I am assuming, and would have to look individually, that these sites were probably cooperative in coming into documentary compliance.

Mr. STUPAK. After your audit, tab number 26.

Dr. CHEW. It could have been after the audit or the monitoring, because the monitoring was in parallel.

Mr. STUPAK. OK. At any time after tab 26, October of 2002, did Aventis contact the FDA and tell them, We have trouble with this Study 3014 and it may be based on fraudulent activities?

Dr. CHEW. To my knowledge, the team that was looking at this felt that they had addressed many of the issues of GCP noncompliance. And when the auditor came from FDA to look at Dr. Kirkman-Campbell's site specifically over a 9-day period from October 15th to the 24th, the documentary evidence of that audit corroborated many of the same GCP violations that were found by the team.

Mr. STUPAK. Great. But my question was did Aventis, after October of 2002, notify the FDA of problems? We are not just talking about Kirkman-Campbell. October of 2002 has nine other sites, and every one of them had significant issues that needed corrective action. Did Aventis notify the FDA of these other sites that had significant issues that needed corrective action?

Dr. CHEW. To my knowledge—and I would have to review—I don't think so.

Mr. STUPAK. OK. Where does your responsibility come in, then, when you appear before the FDA and the FDA advisory committee, to tell the FDA that you have had significant problems with the 10 sites—the only sites you audited, all 10 of them had significant problems that needed corrective action—when is it your responsibility to let the FDA know?

Dr. CHEW. Are you talking about hypothetically or this specific trial?

Mr. STUPAK. I am talking about Aventis here and on this Ketek. When did you have that responsibility?

Dr. CHEW. Of course, we do things differently now with the new company.

Mr. STUPAK. I know everyone does everything different now, but—

Dr. CHEW. But at that time, at that time it is my understanding the company reviewed these issues with the site, had documented these errors, again in retrospect, and in other words they had addressed the issues as best they could in a retrospective fashion.

Mr. STUPAK. Dr. Chew—

Dr. CHEW. Yes.

Mr. STUPAK. The answer is just that. Look. After October of 2002, you did nothing to notify FDA of the problems with the integrity of Study 3014. Did Aventis? They did not, did they?

Dr. CHEW. I believe Aventis felt that the trial had integrity.

Mr. STUPAK. That's not what I asked. OK. You think this is—you believe this has integrity, this 3014 has integrity?

Dr. CHEW. I am sorry, could you repeat that? I am sorry.

Mr. STUPAK. Sure. After October 2002—

Dr. CHEW. Yes.

Mr. STUPAK [continuing]. After your audit, 10 sites, every one of them has significant issues that need corrective action, you never notified the FDA of possible integrity issues with Study 3014.

Dr. CHEW. The FDA had opened up a criminal investigation.

Mr. STUPAK. That's not what I asked.

Dr. CHEW. But to my knowledge, there had been no notification, because it is my review of the record that these issues with these other sites had been addressed in terms of memos to file. An inadequate approach—

Mr. STUPAK. Memo to file from who, Aventis to Aventis?

Dr. CHEW. The memos to file would usually be the investigator going to the file.

Mr. STUPAK. In other words, your investigators going to your files?

Dr. CHEW. No, this would be at the site. So that they could be audited and reviewed by auditors. The specific point being to have the documentation.

Mr. STUPAK. They could be. But what is your responsibility here? October 2002, 10 sites, every one significant problems, need corrective action. Did you notify the FDA about that? That's all I am asking you.

Dr. CHEW. At that time, the answer, to my knowledge, is no.

Mr. STUPAK. OK. So even though you submitted this study, you never told the FDA that of the 10 sites that were audited you had significant issues with?

Dr. CHEW. It is my understanding that these issues had been addressed at the time they were documented at previous monitoring.

Mr. STUPAK. Who addressed these issues? Aventis, right?

Dr. CHEW. Typically, the PPD would identify these issues, report them to Aventis, and the site would be instructed to document what had happened.

Mr. STUPAK. Sites were already closed. We have established that. That is already closed.

Dr. CHEW. When it came to the monitoring, as usual in any trial when there is monitoring, the issues have to be fixed and corrected. The enrollment had stopped, but the sites may still have been in the process of regulatory and document assembly. So we have to separate out the enrollment of patients, which is 3 months, and the monitoring that went on for much longer, obviously.

Mr. STUPAK. Why do you do an audit?

Dr. CHEW. The audit is to generally look at processes to see if the processes have been fulfilled.

Mr. STUPAK. And of these 10 audits, every one of them failed.

Dr. CHEW. Of these high enrolling sites, there were significant issues requiring action.

Mr. STUPAK. Isn't an audit to help determine the integrity and the quality of the study you are doing?

Dr. CHEW. There is more than auditing to do that, but auditing is part of it.

Mr. STUPAK. Correct. And you batted a big zero on that one, so there is a serious question about the quality of the report, then, is there not, of the study you are doing?

Dr. CHEW. From my understanding, these issues were found and identified. It was not a blemish-free trial. These issues were identified after the patients had come through the trial. But it is my understanding—

Mr. STUPAK. What was your revenue, what was Aventis's revenue from Ketek back in 2005?

Dr. CHEW. I would have to find that out.

Mr. STUPAK. 264 million sound right?

Dr. CHEW. I would have to document that.

Mr. STUPAK. You have any reason to dispute 264 million?

Dr. CHEW. No, I just have no primary knowledge of that number.

Mr. STUPAK. I see. A year ago the FDA finally removed bronchitis and sinusitis from the labeled indications for Ketek, leaving only pneumonia as an authorized use for the drug. Is that correct?

Dr. CHEW. That's correct.

Mr. STUPAK. Is Sanofi-Aventis still detailing the drug to doctors?

Dr. CHEW. To my knowledge, no, there is no promotion.

Mr. STUPAK. OK. Your auditors were at Kirkman-Campbell's site one week before the FDA investigator who told the congressional staff that Kirkman-Campbell's site was the worst she had seen in 25 years. How did your auditors miss the fraud there at Kirkman-Campbell?

Dr. CHEW. It was the auditors who identified, in January I think, 17th, 18th, 2002, that there was a potential problem; additional monitoring needed to be done. That's where PPD was sent on February 18th, 19th and 21st. There were additional visits April 1 through 5. There were 165 calls to this site. There was extensive attention paid to this site.

Mr. STUPAK. Right. And did you disclose all that to the FDA?

Dr. CHEW. Well, no. The answer is no because the issues were addressed and documented for the file. And it is my knowledge that this was also documented by the 483 that was issued on October 24th by the FDA auditor.

Mr. STUPAK. I asked the other investigators, I guess it is only fair to ask you—let me find it here—the statute of limitations on the possibility of indicating Aventis for fraud in connection with Study 3014, when the investigators were kicking around the date, since the approval was, I believe, April 1st, 2004 for Ketek?

Dr. CHEW. That's correct.

Mr. STUPAK. And if that approval is based upon fraud, fraudulent Study 3014, do you think Aventis is liable then for fraud?

Dr. CHEW. Can I answer that by it's my understanding that FDA did not rely on 3014 for its approval, having 14 clinical trials, also having the German registry, and at that time 4 million patients' use. So it is my understanding that 3014 was not used.

Mr. STUPAK. But Aventis, in submitting Study 3014 to the advisory panel, which I believe was on March 25th—not advisory, the advisory—

Dr. CHEW. September 15th and 16th, 2006.

Mr. STUPAK. OK, January. Why did you present Study 3014 to show the efficacy and the safety—

Dr. CHEW. Are you talking about the second advisory committee? Is that right? 2003?

Mr. STUPAK. Yes. Yes.

Dr. CHEW. Right.

Mr. STUPAK. Why did you submit 3014, which showed the efficacy and the safety of Ketek, was it not, for bronchitis, for sinus, and for pneumonia, correct?

Dr. CHEW. The primary was safety. Efficacy had been established according to the first advisory committee with the 14 pivotal trials of phase 3 and those three indications.

Mr. STUPAK. OK. So you submitted for safety. Correct?

Dr. CHEW. Yes.

Mr. STUPAK. OK. And if there is fraud in that safety, would you then agree with us the statute of limitations run on possibly indicting Aventis for fraud in connection with the safety of Study 3014?

Dr. CHEW. I can't comment on this legal term. I am not competent to do that. But at the time of the submission, it is my review, that Aventis felt that this was a trial that was useful and that the issues of good clinical practice had been addressed.

Mr. STUPAK. Useful. You said useful. But when you submitted, you thought that Study 3014 showed the safety of Ketek.

Dr. CHEW. At that time—

Mr. STUPAK. Yes.

Dr. CHEW [continuing]. It is my understanding that this was submitted as a useful response to the request of the first advisory committee for a large safety study. And that was done.

Mr. STUPAK. And it was submitted for the verification of the safety of Ketek for these three problems: sinus, pneumonia, bronchitis.

Dr. CHEW. It was to get additional information as part of other experiences, but it was to provide a large safety experience for Ketek in those three indications, compared to a commonly used antibiotic.

Mr. STUPAK. Mr. Shimkus for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman. And I am not going to be that long. You have spent a lot of time.

Mr. STUPAK. I have more questions.

Mr. SHIMKUS. I am sure here they are waiting for them, too.

I do want to follow up with what the Chairman mentioned, the 10 sites out of 1,800 sites. You know, when we in any—I have got an engineering background to some extent, although I am a politician. And polling is an important aspect of our job and what we do. Of course we are having a lot of polling now with the Presidential race. There are legitimate polls and there are illegitimate polls, and it is based upon how really the science is conducted by the sample size, the randomness, and all the other aspects.

Is there any such standard as to what is an acceptable universe of study on percentages when you have—this is for Dr. Chew—when you pull out 10 sites out of 1,800 sites?

Dr. CHEW. It is my feeling—I am not a statistician—there should have been more sites audited. The pattern in this case, though, of the 10 sites that were audited, is that they were chosen because of their higher enrollment. And high enrollment, as you might suspect, is where people who might commit fraud, especially for monetary gain, may be concentrated. So it may not be truly a random

sample of the 1,800 sites; it is 10 out of 1,800, but it is the high enrolling sites.

Mr. SHIMKUS. Yeah. If all those sites had problems, then what does it tell you about the process of choosing the 10 sites?

Dr. CHEW. About choosing? Well, I think it is more than choosing. It is the training, and it has to be more in time monitoring. You can't show up after the trial is over. So it is selection, training. These are all the things that are done now. And more in time monitoring. Putting a cap on enrollment. And you don't go above that cap until you have had your data validated.

Mr. SHIMKUS. If we have identified, obviously, a problem, let's go back to the basic premise of the initial question again. A credible poll has to have a sample size over 300, has to be random, it has to go across the demographics of the particular area. You can't weigh it to one side over another. How do we get a credible scientific sample, or is there a formula by which we would be deemed legitimate?

Dr. CHEW. You are talking in general?

Mr. SHIMKUS. Yeah. Because part of this is identifying this error.

Dr. CHEW. Right.

Mr. SHIMKUS. But also part of oversight is identifying this error so we can make sure these errors do not happen in the future.

Dr. CHEW. Sure.

Mr. SHIMKUS. So how do we make—how do we ensure that there is legitimate randomness and a sample size big enough that covers? I think most people would say 10—I guess the point is, a number of enrollees in a site may affect that, but still 10 out of 1,800 sites, I think just a casual observer would say, well, no wonder there's problems.

Dr. CHEW. I am not a statistician. I don't think 10 is enough. This was not a random sample. This is where the high enrollers were. And I believe that the FDA also takes a similar approach, which is to go where the high enrollers are because—

Mr. SHIMKUS. Just because the FDA does something doesn't—

Dr. CHEW. No, no, I am not saying. I mean that is where you are likely to find problems. It is not a random sample. I think a random sample, of course, would choose these sites randomly in terms of the demographics either by the type of doctor, the type of illness. It would probably have to be on a case-by-case basis and would have to be truly random, not skewed toward one end of the enrollment spectrum, because you may find the problems there but then attribute that to the whole sample.

Mr. SHIMKUS. The other aspect, I was county treasurer at one time for 6 years. And one basic management principle is management by walking around, which means you walk around all your employees' offices, you visit with them, you see them, you see what is on their desks, you come at different times. Visiting 10 sites out of 1,800 sites on a research isn't really perceived—would be perceived as good management by walking around when you are talking about the health and welfare and the safety and the efficacy of drug testing. And so maybe there is an attempt or we need to be more specific on a formulary basis about where we have to be and in what numbers and in what percentages and the like.

Dr. CHEW. Well, you know, the auditing is to be different from the monitoring. And I did want to clarify that. Monitoring of these 1,800 sites was that—I believe 99.6 percent, a very high number of sites that recruited 15 or more were visited physically. And I believe that—and that accounts for 80 percent of the patients.

There were also weekly phone calls to all the sites, 26,000 phone calls in this trial. And apart from the weekly status, there were additional phone calls, of course, as the need arose, to over 90,000 phone calls. And overall, I believe approximately 58 percent of the sites, more than 900 during the study, received on-site visits.

Now, those are the statistics. But the issue was the trial recruited so fast that I believe most of the visits occurred after the randomization and treatment period had gone through. So monitoring ideally should be not only an educational training repair process for patients who have been through, but for patients yet to come. That did not occur in 2014, and that is what has been changed for the large trials that Sanofi-Aventis is doing now—for all trials that Sanofi-Aventis is doing now.

Mr. SHIMKUS. If these 10 were the top sites, if they were the top sites you could almost conclude that most sites had problems, then.

Dr. CHEW. Well, I think it is hard to say that, because it is the expectation that the high enrolling sites, if there is monetary reward as the goal for the fast enrollment and the high enrollment, may concentrate or be where the issues may concentrate. It is not a random sample. It is everything but a random sample. It is the highest enrollers out of 1,800.

Mr. SHIMKUS. When you get this information, what is the conclusion that you draw about the integrity of the whole thing? What would be the conclusion then?

Dr. CHEW. As I said, I think it is investigator selection, training, retraining, monitoring. And you got to get on top, you got to get on top—

Mr. SHIMKUS. The conclusion would be the data integrity was not solid.

Dr. CHEW. The data integrity was looked at not only by what was found, but what was done about it. Now, as we said, what was done about it was to document in retrospect, because in most cases the monitoring occurred after the thing. So that if you had a high enrolling site, it is likely that you would not have gotten out there to stem the bad practice. So when you got there it would be documenting with memos to file. Not adequate, very helpful, but in this case not adequate because it was retrospective.

Mr. SHIMKUS. Dr. Eshelman, I saw you nodding or showing some signs along this line of questioning. Is there something you want to add? What about data integrity? And what conclusions should have been drawn?

Mr. ESHELMAN. No, sir, I didn't have anything to add on that particular issue. As it goes to data integrity. I think that is a case-by-case basis and determination made by the sponsor of the trial. I spent some time in big pharma prior to my CRO experience, so I am familiar with what goes on there as well, what the requirements are, what the standards are and so forth. And, you know, this case notwithstanding, it has always been my experience over the years that the sponsors, the CROs, everybody, is after data in-

tegrity. We know what we are here for. And the down side of not doing that is so steep that only a fool would go there, in my view.

Mr. SHIMKUS. I would like to follow up with you on the monitoring plan for this Study 3014. Was there dedicated sufficient resources for the implementing of the program?

Mr. ESHELMAN. By whom?

Mr. SHIMKUS. By you.

Mr. ESHELMAN. By PPD?

Mr. SHIMKUS. Yeah.

Mr. ESHELMAN. Actually, I was on the phone over the weekend with the person who was the project coordinator at PPD for this trial, and I put that very question to her. I said, Were you adequately resourced? And she said, yes, at the beginning of the trial that she felt like she was adequately resourced. We were resourced to the contractual requirements and so forth.

But to Dr. Chew's point, I think certainly PPD, and it sounds like perhaps Aventis as well, underestimated the workload that was suddenly going to appear here because of the 24,000 patients, how quickly they were randomized. And I think more importantly, perhaps in this instance, as it has to do with short-term therapy on an antibiotic, by the time some of the problems are identified and so forth, the therapy is so short that you really don't have time to make some corrections in real time. And therefore, you are doing it after the fact. This was also targeted monitoring.

So by definition we were not going to look at every site in every case and so forth as you might do in a standard phase 3 trial. So, you know, in retrospect, in some respects we were almost set up for some of these problems.

Mr. SHIMKUS. And finally, on the resource question, did Aventis give you all the tools you needed to do your part?

Mr. ESHELMAN. Yes. I think so.

Mr. SHIMKUS. And let me just add—I am going to end with this, Mr. Chairman—back to Dr. Chew. I would like to discuss the research and development of antibiotics. Since Ketek's approval, how many antibiotics has Sanofi-Aventis developed or begun to develop?

Dr. CHEW. None. There may be something very early, but there is nothing in the late stage.

Mr. SHIMKUS. Has the company's experience with this study, especially 3014 and the events thereafter, caused it to reduce its research and development efforts and develop new antibiotics?

Dr. CHEW. Well, I don't want to speak about the antibiotic program in general. Let me say that R&D has always been challenging. We realize that this is a heavily regulated industry, as it should be. I only got involved in this personally, because of my own commitment as a physician, to go beyond individual patient care to broader patient care. So we recognize the hurdles are high, and we have not reduced R&D development in general.

Mr. SHIMKUS. Thank you, Mr. Chairman.

Mr. STUPAK. Thank you, Mr. Shimkus. Thanks for getting here. I know it has been a hassle today.

Dr. Eshelman, if I say that right, adequately resourced; PPD was paid close to \$30 million to do their work here, were they not?

Mr. ESHELMAN. My recollection is the payment for direct costs was somewhere around 20, and the pass-through costs, in other

words the payments to the physicians, were somewhere around 8. So ours was 20, investigators 8. That is my recollection.

Mr. STUPAK. OK. So \$20 million to do it. What was your response—I asked Dr. Chew, it is probably better to ask you—what was your responsibility as the contract research organization to report the sites to the IRB when there was suspicion of fraud or other problems with this study?

Mr. ESHELMAN. I believe we have such responsibility. And it sounds like, from the testimony of Ms. Price, that in fact a lot of that reporting did occur.

Mr. STUPAK. OK. Nothing would have stopped PPD from alerting Copernicus, correct?

Mr. ESHELMAN. No, sir. I am not aware of anything.

Mr. STUPAK. OK. Did you notify Copernicus of the irregularities and possible forgery found by PPD at the Kirkman-Campbell site?

Mr. ESHELMAN. I assume that we did. And it certainly sounds like there were a number of memos and so forth. I can't comment factually on exactly what we communicated to Copernicus at any given time on the Kirkman-Campbell site, but I assume that this went on.

Mr. STUPAK. Well, Ms. Cisneros worked for you, right?

Mr. ESHELMAN. Yes.

Mr. STUPAK. Made the first telephone call. And I think Ms. Price said 83 other complaints came from the Kirkman-Campbell site and other sites. Did you feel compelled, then, to notify Aventis about all these complaints?

Mr. ESHELMAN. Yes, sir.

Mr. STUPAK. OK. How about the FDA? Did you feel compelled to tell the FDA?

Mr. ESHELMAN. No, sir, not in this case, because of the way the contract read, number one. And number two, there was some debate over whether or not this was to the level of fraud. I think the issue of data integrity that goes along with how you present data to the FDA or otherwise is a determination that has to be made by the sponsor.

Mr. STUPAK. How can you say—in fact, Dr. Chew said the same thing—didn't know if it went to the level of fraud, when the complaint said errors on just about every informed consent, date modifications, initials different from signature, study coordinator entering date for subjects and principal investigator, blatantly forged signature on informed consent, medical records are very limited, use of different color ink on medical charts, overwrites, crossouts, inserts of diagnosis in different color ink, routine failure to give pregnancy tests to women of childbearing years, study investigator and coordinator unaware of the definitions of serious adverse events, no adverse events for the first 300 patients enrolled with drugs known to have adverse events, lab results indicating blood splitting, lack of proper diagnosis for study eligibility, husbands and wives being enrolled together, large number of patients randomized in the interactive voice response system in a short increment of time when the office was closed. I mean, how would that not indicate fraud?

Mr. ESHELMAN. If I could cut to the chase here.

Mr. STUPAK. Yeah, please, I wish someone would.

Mr. ESHELMAN. Had I known in detail at the time what was going on, I would have picked up the phone.

Mr. STUPAK. Whose responsibility is it? I mean we are hearing all these reports of all this stuff going on.

Mr. ESHELMAN. It is mine. It is my responsibility.

Mr. STUPAK. OK.

Mr. ESHELMAN. In fact, I did not have all the facts at my disposal at that time. Had I known what I know now, in retrospect I would have picked up the phone and I would have called—Dr. Chew wasn't there at the time, I don't think—but I would have called someone at Aventis at a high level of authority and expressed my concerns about this. And I believe that if that had occurred there may have been a different response out of Aventis.

Mr. STUPAK. You know Robert McCormick?

Mr. ESHELMAN. Sure.

Mr. STUPAK. Isn't he your Vice President of Quality Management Systems?

Mr. ESHELMAN. Yes.

Mr. STUPAK. He didn't talk to you about this? About all the problems?

Mr. ESHELMAN. Not in detail about the Kirkman-Campbell site at the time.

Mr. STUPAK. Not just Kirkman-Campbell. Any of the problems with the—

Mr. ESHELMAN. Certainly with Dr. McCloud.

Mr. STUPAK. OK. So you knew about it then?

Mr. ESHELMAN. About Dr. McCloud? Yes, I did.

Mr. STUPAK. And about the other problems with Study 3014.

Mr. ESHELMAN. No, sir, I did not know the magnitude of those problems.

Mr. STUPAK. So if Mr. McCormick said he informed you, that wouldn't be right?

Mr. ESHELMAN. Informed me about what?

Mr. STUPAK. About the problems at Kirkman-Campbell and all the other issues involving this study, since you were the CEO of PPD.

Mr. ESHELMAN. No, at the time, I don't think that's correct. I think subsequent to that it certainly is. It certainly is correct with respect to Dr. McCloud. He informed both myself and Dr. Covington. Mr. McCormick, Dr. Covington and myself were in total agreement about how the situation should be handled at Dr. McCloud's site. And in fact, we made a no-name call to the FDA asking for guidance on that issue, and we never—

Mr. STUPAK. Just on McCloud. That's the only one you talked—

Mr. ESHELMAN. Yes, sir. And we never got a response.

Mr. STUPAK. So when McCormick says, tells our staff that it is your policy, PPD's policy, to communicate significant complaints issues to you as CEO and that you are personally made aware of the large-scale irregularities and noncompliance of Dr. Kirkman-Campbell, that is not true?

Mr. ESHELMAN. The policy is certainly correct.

Mr. STUPAK. OK.

Mr. ESHELMAN. It is not my recollection that I knew in detail at the time about Kirkman-Campbell, nor is it my recollection that I understood and appreciated the magnitude of the overall issue.

Mr. STUPAK. Did PPD or anyone on your staff, did they recommend that Aventis call the FDA on these irregularities? Did you advocate—anyone from your company advocate to Aventis that they call the FDA on the irregularities on this study?

Mr. ESHELMAN. I don't know the answer to that.

Mr. STUPAK. OK. Take a look at Exhibit No. 21. It is the one that Mr. Markey had asked about.

Your employee, PPD's employee, is notifying the Aventis study manager, who is no longer with Aventis, that she is receiving conflicting information from sites, including subjects who were never receiving—who never signed informed consents, and subjects who were treated with a different drug than that indicated in the existing database.

And the Aventis study manager says, well, we can't unlock the database. So is it ever acceptable to run with the data when you are unsure if the subject signed the consent form or if the data integrity issues that are listed here remained with the study?

Mr. ESHELMAN. I think generally all of us in this business try to have a pristine database before we lock. So in other words, all of the outstanding queries have been answered and this and that and the other. If, however, you stumble across something post-lock that indicates that, in fact, your procedure was not robust, then generally speaking you unlock the database and you make whatever the corrections are.

Mr. STUPAK. But that didn't happen here. Did anyone unlock the database?

Mr. ESHELMAN. I don't know. I am sorry, I don't know.

Mr. STUPAK. Shouldn't this e-mail have sent a red flag to your company that Aventis was not acting in good faith?

Mr. ESHELMAN. I don't know. I mean I am just not qualified to say. I don't know—I don't have any idea what was going on at Aventis.

Mr. STUPAK. OK. But this is your employee, right?

Mr. ESHELMAN. Yes.

Mr. STUPAK. Who wrote this?

Mr. ESHELMAN. Yes, sir.

Mr. STUPAK. Shouldn't you have done something about it, PPD? You have people that were allegedly in here, but they have no informed consent. This questions the integrity of the study.

Mr. ESHELMAN. It is not our responsibility to dictate to a client what they do or do not put into a submission, nor is it our responsibility generally to dictate to them how they do their analyses.

Now sometimes, as you know, there will be two sets of analyses. There will be an intent to treat that has everybody that ever received the drug, no matter what. OK. And then there will be what we would call a primary set of efficacy and safety data on—

Mr. STUPAK. And this would deal with the primary set of efficacy and safety with this drug, are we not? That was the purpose of this study.

Mr. ESHELMAN. Ordinarily, that's the set of data upon which—

Mr. STUPAK. This study right here. It is safety, right? Wasn't it the main purpose for the study?

Mr. ESHELMAN. Yes, sir.

Mr. STUPAK. OK.

Mr. ESHELMAN. But the primary database, the one that you think is clean, would be the one that ordinarily I think a regulatory body would rely upon if they were going to rely upon the study. And it is my understanding they didn't even rely on this study.

Mr. STUPAK. So what are you saying, you keep two sets of books, you give the FDA the one that's the best for your drug?

Mr. ESHELMAN. No, sir. You give them both the analyses. This is standard practice. Because we want to be sure that we fully report everybody that got the drug for safety purposes. For that very reason, you report all of them.

Mr. STUPAK. But if people in your study did not receive the drug and there is no informed consent, doesn't that question the integrity of the study?

Mr. ESHELMAN. Yes, sir, and therefore there might be more than one analysis done.

Mr. STUPAK. And therefore shouldn't PPD have done something about it, then, since your own employees questioned the integrity of the study?

Mr. ESHELMAN. I don't know what we would have done. We weren't responsible for the submission.

Mr. STUPAK. What is your responsibility then?

Mr. ESHELMAN. Our responsibility was to monitor and to report to the sponsor.

Mr. STUPAK. So outside that, you have no obligation to report to the FDA or anything else that there is some question?

Mr. ESHELMAN. Not in terms of what was sent in a submission. Number one, we would have no way of knowing that.

Mr. STUPAK. And if you think there's questions about the integrity of data that's going to be submitted to the FDA for drug safety, you have no responsibility to contact the FDA and say, Hey, take a closer look at this? I guess it's more an ethical question.

Mr. ESHELMAN. Obviously, if we were in a situation where we thought a sponsor was doing something egregious and they wanted us to be party to that, that would not happen.

Mr. STUPAK. OK. I am not asking to be a party, but if you have knowledge that could go to the question of veracity of the study, that goes to the safety of a drug, do you have a responsibility then?

Mr. ESHELMAN. But it wasn't our determination to make, Mr. Chairman.

Mr. STUPAK. By choice or by contractual obligation?

Mr. ESHELMAN. I think by contractual obligation. I mean we just weren't assigned that responsibility.

Mr. STUPAK. How about company ethics then? Your first bullet in PPD's mission statement says, as it says on your Web site: We will work with pride and unwavering integrity to help our clients accelerate delivery of safe and effective therapeutics to patients.

In this case do you think you lived up to that mission statement? Don't you think you had a responsibility for safe and effective therapeutics to patients?

Mr. ESHELMAN. I think under the conditions, we absolutely did our job in trying to identify departures from GCP, and data integrity issues, and, to some extent, fraud. I think Aventis did so as well with all of their checks and their audits and so forth and so on. To me, the issue of what did or did not get into a submission is—it is related, but it is a different issue.

Mr. STUPAK. Well, I guess it is just not me thinking this. If I may go to Barron's newspaper on November 12th, 2007, it reported that PPD, unlike many CROs, is willing to take a stake in some drugs being tested in exchange for free or cut-price monitoring service. Does that put you in a dangerous conflict-of-interest position? That is, you are essentially monitoring a drug in which you have a financial interest?

Mr. ESHELMAN. Well, first of all, I don't agree with all of that statement in Barron's. We don't do anything in exchange for cut-rate monitoring. I don't know what that means.

But in terms of monitoring studies where we have a financial interest in the drug, I really don't see how that is different from any sponsor monitoring studies because, you know, the drug came out of their research. So I don't see how that is any different.

Mr. STUPAK. But don't you have the—isn't PPD's duty, one other duty in this and in 3014 was to train and select qualified investigators for the study?

Mr. ESHELMAN. Certainly to select. We were not responsible for the training. That was another third-party vendor.

Mr. STUPAK. OK. OK. Were you familiar with the Barron's newspaper report, "The Very Pictures of Health," by Jay Palmer, dated November 12th, 2007, in which they mentioned PPD, unlike other CROs, take a financial interest—

Mr. ESHELMAN. I can't say that I was, because I might have called them up and taken exception to their statement.

Mr. STUPAK. OK. I have nothing further. Mr. Shimkus, anything further?

Mr. SHIMKUS. No, I don't.

Mr. STUPAK. OK. Then we will excuse this panel. Thank you all for coming today. That concludes all the questioning. I want to thank all the witnesses for coming here today, and for their testimony and their information they provided us.

I would note that I am troubled by a number of the answers we have heard today. And accordingly, we will be considering referral of some of the materials to the FDA and to the Department of Justice. I don't think it is just this panel. I think it was all the panels. We had troubles with these witnesses. Overall, I thought it was a good hearing, but many of us here are very troubled at what we heard today.

So with that, I will ask for unanimous consent that the record remain open for 30 days for additional questions for the record. Without objection, the record will remain open.

I ask unanimous consent that the contents of our document binder be entered into the record. Without objection, documents will be entered into the record.

That concludes our hearing. And, without objection, this meeting of the subcommittee is adjourned.

[Whereupon, at 3:39 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

 Assistant Secretary for Legislation
 Washington, DC 20201

February 11, 2008

The Honorable John D. Dingell
 Chairman
 Committee on Energy and Commerce
 U.S. House of Representatives
 Washington, D.C. 20515

Dear Mr. Chairman:

This is in response to your subpoena dated February 1, 2008, seeking materials used to prepare Food and Drug Administration ("FDA" or "Agency") Commissioner of Food and Drugs Dr. Andrew von Eschenbach for his appearance before the Committee at a hearing on March 22, 2007, titled "The Adequacy of FDA Efforts to Assure the Safety of the Drug Supply, Part II." Working with Congress on oversight issues is an important responsibility and high priority for the Department of Health and Human Services (HHS or Department) and its Agencies, including FDA.

On the basis of discussions with your staff, it is our understanding that the present subpoena arises from concerns you first raised following the Commissioner's testimony of March 22, 2007. On March 28, 2007, you wrote raising concerns about the accuracy of certain aspects of the Commissioner's testimony and attached an article from *FDAWebview* that listed 14 instances of what the authors considered to be inaccurate or misleading testimony. (Attachment 1) The Agency promptly assessed the allegations and, on April 4, 2007, provided the Committee with an 11-page detailed response to the *FDAWebview* article. (Attachment 2).

That detailed explanation was followed a week later, on April 11, 2007, by correspondence from Commissioner von Eschenbach to the Committee that provided documentation supporting the April 4 response. (Attachment 3, without enclosures)

Following receipt of the FDA's extensive and detailed response to the issues raised by the Committee and Subcommittee, neither the Committee nor Subcommittee challenged FDA's explanations or raised any additional issues, but nonetheless continued to seek briefing materials used to prepare Commissioner von Eschenbach's testimony. On June 7, 2007, FDA Chief of Staff Susan Winckler wrote to the Committee, resending the April 4 FDA analysis of the *FDAWebview* article and offering a briefing by subject matter experts within the Agency to address any specific questions that might remain. (Attachment 4, without enclosure) That letter also articulated the Agency's concerns about revealing confidential deliberative communications

related to the preparation of testimony before Congress. To date, the Committee has not responded to the offer of a briefing, nor has the Committee articulated why the Agency's response to the 14 alleged errors or misrepresentations was insufficient.

The Committee instead insists that the Department provide: "all records, in unredacted form, prepared for or used in the preparation of the testimony of the Commissioner of Food and Drugs, Andrew C. von Eschenbach, before the Committee on Energy and Commerce on March 22, 2007, by any employee of the Department of Health and Human Services (HHS), including but not limited to—(A) any briefing books and background memoranda; and (B) all communications between and among senior staff of Food and Drug Administration (FDA), the FDA office of Legislative Affairs, the HHS Office of Legislative Affairs, and the HHS Office of General Counsel, including communications from the FDA Office of the Chief Counsel to Commissioner von Eschenbach and his senior staff." (Attachment 5)

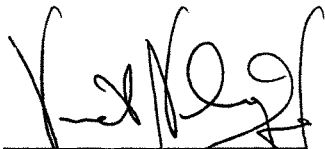
The Department has serious concerns about providing the kind of materials the Committee has subpoenaed. Providing such highly confidential and deliberative materials used to prepare witnesses testifying before Congress risks chilling the open exchange of views that is essential to the effective conduct of Agency business, including its relations with Congress. Such a disclosure would make it very difficult for advisors to provide full and frank advice to Agency officials regarding congressional testimony in the future, knowing that any candid advice or discussion could later be the subject of congressional oversight. As Members of Congress, you no doubt appreciate the need for such advice and discussion. The Department and its various components provide testimony to Congress countless times and it is important that the Department and its component Agencies retain the ability to prepare Executive branch witnesses for testimony before the Legislative branch effectively and in confidence. To do otherwise, would risk depriving the Department, its agencies, and ultimately Congress of the informational needs.

In this particular situation, there are additional reasons to seek alternative solutions. First, the Agency has responded to the concerns raised by the Committee in its March 28, 2007, letter by way of the 11-page analysis sent on April 4, 2007, and followed by additional associated documentation. Second, the Committee has received those communications, haven't raised additional concerns with the responses. Third, the description of documents sought by the subpoena ("all records...") is overly broad. Fourth, the Agency has offered additional accommodations in the form of briefings that provide a better venue for the Committee or Subcommittee to express any remaining concerns and receive information targeted to those concerns.


As you know, HHS has a longstanding policy of complying with Congressional requests for information to the fullest extent consistent with the constitutional and statutory responsibilities of HHS as part of the Executive Branch, including protecting important confidentiality interests. (See Letter to Representative John Linder from Assistant Attorney General Robert Raben, dated January 27, 2000.) (Attachment 6) When HHS faces a difference of views with the Congress concerning whether requested information is producible, the Department seeks to work with the Congress to arrive at an appropriate accommodation or understanding. This longstanding practice of accommodation and understanding has been

recognized by the Judicial Branch as the appropriate process to resolve conflicts between the branches of the federal government. (See *United States v. American Tel. & Tel. Co.*, 567 F.2d 121, 127 (D.C. Cir. 1977)("[E]ach branch should take cognizance of an implicit constitutional mandate to seek optimal accommodation through a realistic evaluation of the needs of the conflicting branches in the particular fact situation.")

Consistent with its responsibilities as part of the Executive Branch, the Department has offered accommodations to try to meet the Committee's oversight needs while preserving equally important Executive Branch interests. In light of the Department's concerns about turning over highly confidential and deliberative materials used for preparation of testimony before Congress, the Department again proposes as an accommodation a briefing by subject matter experts related to your ongoing concerns.


 Vincent J. Ventimiglia, Jr.
 Assistant Secretary for Legislation
 Department of Health and Human
 Services

Thank you,


 Susan C. Winckler
 Chief of Staff
 Food and Drug Administration

Attachment 1

HENRY A. WAXMAN, CALIFORNIA
 EDWARD J. MARKEY, MASSACHUSETTS
 ROSE KOLCHER, VIRGINIA
 EDOLPHUS TOMLIN, NEW YORK
 FRANK PALLONE, JR., NEW JERSEY
 BART GORDON, TENNESSEE
 ROBERT L. RUSS, ILLINOIS
 ANITA B. BISHOP, CALIFORNIA
 BART STUPAK, MICHIGAN
 ELIOT L. ENGLISH, NEW YORK
 ALBERT R. WYNN, MARYLAND
 GENE GREEN, TEXAS
 DIANA PIRONETTE, COLORADO
 MICK COZANSKY
 LOIS CAPPS, CALIFORNIA
 MARK DOYLE, PENNSYLVANIA
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 G.E. BUTTERFIELD, NORTH CAROLINA
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 JOHN BARTON, GEORGIA
 SARON P. HILL, INDIANA

DENNIS K. FITZGERALDS, CHIEF OF STAFF
 DOREA A. ROTHSCHILD, CHIEF COUNSEL

ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515-6115

JOHN D. DINGELL, MICHIGAN
 CHAIRMAN

March 28, 2007

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 MARSHA BLACKBURN, TENNESSEE

The Honorable Michael O. Leavitt
 Secretary
 U.S. Department of Health and Human Services
 200 Independence Avenue, SW
 Washington, D.C. 20201

Dear Mr. Secretary:

On March 22, 2007, the Food and Drug Administration (FDA) Commissioner Andrew von Eschenbach testified under oath before the Subcommittee on Oversight and Investigations regarding our investigation into the adequacy of the FDA's efforts to protect Americans from unnecessary risks of prescription drugs. At that hearing, questions were raised about the accuracy and candor of his testimony and prepared statement. As you can see from the attached news article, others who attended the hearing and had first-hand experience with some of the events described in his testimony have also raised questions about whether the Commissioner or those who helped prepare his testimony intentionally mislead the Subcommittee.


We take such allegations seriously. Accordingly, we request that you provide all documents prepared for or used in the preparation of Dr. von Eschenbach's testimony by any employee of the Department including, but not limited to, any briefing books, background memoranda and all communications between and among the senior staff of the FDA, the Offices of Legislative Affairs of the FDA and the Department of Health and Human Services (HHS), the HHS Office of General Counsel, including the Office of Chief Counsel to FDA and Commissioner von Eschenbach and his senior staff. These records must be delivered by no later than close of business on Wednesday, April 4, 2007, to room 316 of the Ford House Office Building, U.S. House of Representatives.

Further, please have all senior staff and counsels who participated in the preparation of the testimony submitted on March 22, 2007, make arrangements to be interviewed by the Committee staff in room 316 of the Ford House Office Building during the week beginning Monday, April 9, 2007. Please inform these individuals that they have a right to be accompanied by personal counsel. No employees of the Department will be allowed to participate in the interviews.

The Honorable Michael O. Leavitt
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Arrangements may be made by contacting Kyle Chapman or Rachel Bleshman of the Committee staff at (202) 226-2424. If you have any questions relating to this request, please contact John Sopko, Chief Counsel for Oversight, or David Nelson, Senior Investigator, with the Committee on Energy and Commerce staff at (202) 225-3641.

Sincerely,


John D. Dingell
Chairman
Bob Stupak
Chairman
Subcommittee on Oversight and Investigations

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Ed Whitfield, Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce

ATTACHMENT

From *FDAWebview* March 26, 2007

FDA commissioner Andrew von Eschenbach made 11 false statements and three "misleading" ones in his sworn testimony to the House Oversight and Investigations Subcommittee last week, according to a detailed critique provided by whistleblower David Ross. His allegations, to do with the Sanofi-aventis antibiotic Ketek's approval, are believed to be being taken very seriously by subcommittee chairman Bart Stupak (D-MI). A former state trooper, Stupak has already subjected von Eschenbach to ~~grilling and skeptical questioning~~ over his "false" testimony, and has indicated he plans calling the commissioner back to explain in the presence of Sanofi-aventis.

In a ~~page-by-page critique~~ he provided to the subcommittee, supported by internal FDA emails between Ketek reviewers and senior managers, including Office of New Drugs deputy director Sandra Kweder, Office of Drug Evaluation IV director Mark Goldberg and CDER's Division of Scientific Investigations, Ross counted these von Eschenbach statements he said were false:

1. Ketek's data problems were only in one large study. Emails and FDA-483s as early as a 12/19/02 face-to-face meeting with the company substantiated that at least three sites were then known by both FDA and Sanofi-aventis to have serious problems, and a fourth site with problems came in within a week of that date.
2. That study, known as 3014, "had to be disregarded." Emails substantiate that it was not disregarded, and adverse event data from it were used, according to Kweder, to "qualitatively assess patterns of toxicity."
3. The adverse findings about 3014's data were "quite preliminary" at the time of the 1/8/03 advisory committee meeting that recommended Ketek be approved. False, says Ross, because at that time FDA had issued FDA-483s.
4. At the time of the advisory committee meeting, FDA believed "based on the best information available to us, that the concerns applied to only one site out of more than 1800." Completely false, says Ross, citing seven internal emails, because at least four sites were then implicated.
5. The compromised data were too preliminary to be presented to the advisory committee. Ross, however says this testimony was also false because "the director of the review office stated that it would not be 'productive' to present the data integrity concerns to the committee, not that the findings were preliminary."

6. Von Eschenbach testified that FDA had noted that the final decision regarding approval of each indication would be made after a review of the information and analyses requested in another approvable letter sent to Sanofi-aventis after the advisory committee meeting. False, says Ross, because this letter asked for detailed data integrity information but there is no record FDA ever reviewed it.
7. Von Eschenbach repeated later in his testimony that Study 3014 was dropped for consideration in making the decision to approve Ketek, but this was contradicted by Kweder's email.
8. Von Eschenbach said limitations, such as under-reporting, were taken into account in assessing the data derived from foreign post-marketing experience reports. But Ross says the medical officer did not take them into account because their quality was too poor—he "simply ignored the problems."
9. The commissioner's sworn testimony said that although "one case of liver failure that resulted in death was found, it was not clear that this represented a signal beyond what had been seen in the data available at the time of approval." False, says Ross, because "this was exactly the signal that reviewers had been concerned about during the review."
10. Three cases of serious liver toxicity, including one death, were described by von Eschenbach as having been previously reported to FDA, "although in less detail, making conclusions about them difficult to reach until the published information was available." But Ross says a 1/23/06 email from the medical officer responsible for Ketek said the reporting physician about these cases "gave an extremely detailed report to FDA; the company gave a very sparse report."
11. Von Eschenbach testified "On February 12, 2007, FDA acted on the recommendations of the joint panel and announced revisions to the labeling and indications for Ketek designed to improve the safe use of Ketek by patients." This, Ross says, was false because FDA "failed to institute the panel's recommendation that visual adverse events receive a black box warning."

Although it is a rare step for Congress to take, and Stupak's own comments during last week's hearing suggested he is willing to blame von Eschenbach's subordinates for his false testimony under oath, perjury before Congress is a felony and can be treated as such. Sources close to the situation say the least that von Eschenbach should do now that his testimony has been so exposed is to "ream out" the subordinates who helped him prepare it and demonstrate to the subcommittee how it can't happen again.

Unfortunately, the management culture at FDA — or, to be fair, at other agencies everywhere — is not known for this kind of internal, transparent rigor when senior people have been found to have erred. In case after case over the years, going at least as far back as the Generic Drug Scandal of the late 1980s, colleagues circle the wagons and stonewall their accusers until they go away — as they usually do. Only legislative oversight and the bright light of publicity seem able to alter this syndrome, but their performances have been patchy and inconsistent, which is why the behavior continues. Different players, same game.

Attachment 2

Acknowledging and respecting the importance of Congressional oversight, FDA writes in response to your letter dated March 28, 2007, regarding allegations of inaccuracies in the written testimony that FDA Commissioner Andrew von Eschenbach submitted to Congress on March 22, 2007.

FDA recognizes the serious nature of the allegations listed in the attachment to your letter. We take our obligations to your Oversight Committee very seriously, and we strive to be clear, factual, and forthcoming in our written and oral testimony. We assure you that Dr. von Eschenbach's testimony was prepared with that in mind.

We believe that rather than reflecting an absence of candor or accuracy in the testimony, the allegations in the March 26, 2007 *FDAWebview* article set forth in the attachment to your letter ("trade press attachment") reflect a disagreement with FDA about the scientific and regulatory judgments made by the FDA managers who handled the review of Ketek. FDA has long acknowledged that Ketek involved complex issues and posed difficult regulatory questions for the agency. At the hearing on March 22, 2007, Dr. von Eschenbach described how hindsight has given us an opportunity to re-evaluate some of the decisions we made and to consider what, if anything, the agency might have done differently or better. Furthermore, the testimony was an attempt to characterize in a short written statement a series of discussions and events that took place over several years and to explain the agency's thinking about the events. During the period of time over which the agency considered Ketek, different staff members have held and expressed a variety of views, and some individual views have evolved over time as more information became available.

It is our position that all of the allegations made in the trade press attachment are without merit. Nevertheless, in reviewing the testimony to respond to the allegations, we have identified several phrases that we wish to correct and/or clarify. We apologize for any inadvertent confusion these phrases may have caused.

In the following discussion, we attempt to clarify the agency's testimony with respect to each of the allegations made. For purposes of clarity, we have repeated each of the allegations in the trade press attachment, below (bolded language is directly from the trade press attachment), followed by our response:

1. Trade Press Attachment Issue: Ketek's data problems were only in one large study.

Allegation: Emails and FDA-483s as early as a 12/19/02 face-to-face meeting with the company substantiated that at least three sites were then known by both FDA and Sanofi-aventis to have serious problems, and a fourth site with problems came in within a week of that date.

Response: FDA's testimony on this issue is accurate. The discussion in the written testimony about data integrity concerns did in fact relate to one study, 3014. It is possible, however, that the trade press attachment meant to use the term "site" rather than "study" to suggest that FDA's testimony focused exclusively on the problems in the Kirkman-Campbell site when in fact

additional sites had been inspected (or were being inspected) at the time of the January 8, 2003 Advisory Committee meeting on Ketek.

Even if this were what was meant, the allegation that the testimony was false is clearly incorrect. In two places, the written testimony explicitly noted deficiencies at more than one site. The paragraphs of FDA's written testimony that are most relevant to the allegation appear under the section entitled "Second Cycle:"

Shortly before this planned meeting, CDER's Division of Anti-Infectives and Ophthalmology Products (the Division) started to see preliminary results of inspections of clinical investigation sites from Study 3014. This began with information about the site with the highest enrollment that raised substantial concerns about data coming from that site. Shortly thereafter, results from investigations at other sites also showed deficiencies, though not nearly as concerning as those that had arisen in the first inspection. As this information began to come to light, in accordance with normal practice, the Division met with the sponsor. The sponsor informed the Division that it was aware of some data irregularities and concerns about processes at the first site and assured FDA that there were no similar problems at any other sites.

Please note that at the time of the January 8, 2003, Advisory Committee, inspections had occurred at only three of approximately 1800 sites, and the findings at that time were quite preliminary. To avoid compromising any ongoing investigation, it is Agency policy not to publicly disclose even the existence of a pending investigation. Therefore, we could not discuss the data integrity issues of Study 3014 at the public Advisory Committee meeting. However, we also believed, based on the best information available to us, that the concerns applied to only one site out of more than 1800. It is not unusual for data from some sites to be eliminated from a study but to accept data from the other sites. At the time, there was less information about the other sites under investigation.

The written testimony plainly acknowledges that, at the time of the January 8, 2003, Advisory Committee meeting, inspections had occurred at three of the over 1800 sites in Study 3014. These were the three sites identified by the review division for inspection and the same sites referenced by CDER's Division of Scientific Investigation (DSI) in its January 21, 2003 Clinical Inspection Summary. They are also the only three sites identified in Dr. Ross's team leader review. At the time of the Advisory Committee meeting, however, DSI was still evaluating the inspection results for the three sites. In fact, DSI's formal recommendations with respect to whether data from these three sites could be used in support of the NDA were not presented to the review division until January 21, 2003, almost two weeks after the Advisory Committee meeting.

Thus, at the time of the Advisory Committee meeting, CDER's review division was aware that three sites had been inspected. Through its discussions with DSI, the review division was aware that there appeared to be very serious problems at the Kirkman-Campbell site. Indeed, even though the final DSI report was not yet complete, ORA referred that site to FDA's Office of Criminal Investigation on or about October 24, 2002. With respect to the other two sites, however, the preliminary feedback given to the Division before the Advisory Committee meeting suggested the problems at those two sites were not as serious as those associated with the Kirkman-Campbell site.

In addition, in the case of large multi-center studies like Study 3014, it is not unusual for FDA to exclude a portion of a study based on data integrity concerns at selected sites. At the time of the Advisory Committee meeting, the review division was aware of problems at three sites, but not

yet aware how data integrity problems would affect Study 3014 as a whole. Eventually, and after additional inspections, DSI concluded that data integrity problems cast doubt over the whole study, and, on the strength of that conclusion, the review division did not rely on Study 3014 to support approval of the NDA. As of January 8, 2003, however, final conclusions about the three individual sites or the study as a whole had not yet been reached.

Given this backdrop, the statement in the same paragraph of the written testimony that FDA's "concerns applied to only one site out of more than 1800" must be read in context. The point of the statement was to emphasize that, at the time of the January 8, 2003 Advisory Committee meeting, one site stood out from the others. This was the site that had been referred to the Office of Criminal Investigations, and the site that was of greatest concern to the division at the time. The trade press attachment refers to inspections at four sites. At the time of the January 8, 2003 Advisory Committee meeting, the review division was aware that three sites had been inspected. These are the three sites discussed in the formal clinical inspection summary of January 21, 2003 from DSI. Some of the seven internal e-mails cited as supporting this allegation mention other sites about which DSI had received allegations of impropriety, but these sites had not been inspected at the time of the Advisory Committee meeting.

The review division recently learned that a fourth Study 3014 site, not mentioned in the seven e-mails, had been inspected beginning on November 20, 2002, before the Advisory Committee meeting occurred. The review division had not requested that inspection. Instead, DSI initiated the inspection as a result of information provided by the sponsor. The site enrolled fewer than 10 patients, so it was not one of the eight high enrollment sites on which DSI based its conclusion that the data in Study 3014 could not be relied upon. We note that, as described in the responses to allegations #2 and #6 (below), the review division acted on DSI's conclusions and did not rely upon Study 3014 to support the approval of Ketek.

2. Trade Press Attachment Issue: That study, known as 3014, "had to be disregarded."

Allegation: Emails substantiate that it was not disregarded, and adverse event data from it were used, according to Kweder, to "qualitatively assess patterns of toxicity."

Response: FDA's testimony on this issue is accurate. Study 3014 was disregarded in that it was not used or relied upon to support the approval of Ketek as safe and effective for its intended uses. Although FDA did not rely on Study 3014 to support approval, we reviewed the study for safety findings and adverse event profiles of the drug. Even data from a flawed study such as Study 3014 can provide information that might help to detect a serious safety concern. In other words, data from Study 3014 was reviewed, but in a manner that could only hurt the prospects of Ketek's approval, and it was not relied upon to support approval. This is consistent with FDA's written testimony.

With respect to the review timeline, please note that the division reviewed Study 3014 during the so-called "second cycle" and, based on the data integrity concerns, requested additional data in the second approvable letter, which FDA sent to Sanofi-Aventis on January 24, 2003. In the third cycle, FDA reviewed additional information provided by the sponsor in response to the data integrity issues identified in the January 24 approvable letter. Only near the end of the third

cycle, after receiving DSI recommendations on data integrity related to Study 3014 in a memorandum dated March 25, 2004, did the review division decide to disregard the study completely as a basis to support approval. However, the division had already reviewed the study for safety findings and adverse event profiles of the drug and would have considered serious safety findings adverse to approval.

3. **Trade Press Attachment Issue: The adverse findings about 3014's data were "quite preliminary" at the time of the 1/8/03 advisory committee meeting that recommended Ketek be approved.**

Allegation: False, says Ross, because at that time FDA had issued FDA-483s.

FDA's testimony on this issue is accurate. Form FDA-483s reflect quite preliminary findings. As described in Chapter 5 of FDA's Investigations Operation Manual, Form FDA-483s are issued to a firm's management by the investigator at the end of an establishment inspection before leaving the premises to document the regulatory observations made by the investigator, as required by section 704(b) of the Federal Food, Drug, & Cosmetic Act, 21 U.S.C. 374(b). We note that the Form FDA-483s issued by FDA bear the following statement: "THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE." Before a determination is made about whether any regulatory action is warranted, the observations in a Form FDA-483 and, typically, the evidence on which they are based, are reviewed by managers -- in this case, by managers in CDER's Division of Scientific Investigations. Until they are reviewed by appropriate managers and a classification issued for the inspection, the observations on a Form FDA-483 are considered preliminary findings and not conclusive.

4. **Trade Press Attachment Issue: At the time of the advisory committee meeting, FDA believed "based on the best information available to us, that the concerns applied to only one site out of more than 1800."**

Allegation: Completely false, says Ross, citing seven internal emails, because at least four sites were then implicated.

Response: FDA's testimony on this issue is accurate. This appears to be the same assertion set forth in allegation #1 (above). Accordingly, please see our prior response.

5. **Trade Press Attachment Issue: The compromised data were too preliminary to be presented to the advisory committee.**

Allegation: Ross, however says this testimony was also false because "the director of the review office stated that it would not be 'productive' to present the data integrity concerns to the committee, not that the findings were preliminary."

Response: FDA's testimony on this issue is accurate. There is nothing inconsistent in the e-mail referred to.

The statement made by the Office Director that a discussion of the data integrity issues would in general not be productive was not meant to be a comprehensive rationale for the reasons for making that decision. Rather, the statement was a shorthand expression (contained in a brief e-mail message) of at least two significant concerns. First, at that time, the Office Director believed it was important for the Advisory Committee to learn about the safety data from Study 3014, including reports of hepatic adverse events and abnormal liver function tests in patients treated with Ketek and additional reports and information on a unique visual adverse event, which had been detected in earlier controlled clinical trials. At the same time, the data integrity issues in Study 3014 had not been fully considered and, as described in the response to allegation #1 (above), it was not yet clear whether some of the data in Study 3014 might still be relied upon. In light of these facts, and given the substantial amount of adverse event data contained within study 3014, the Office Director believed it was appropriate to share this information with the Advisory Committee even while FDA continued to assess the integrity of the data in Study 3014.

Second, as described in the written testimony, the Office Director did not want to compromise the ongoing investigation of the 3014 study sites. The Office Director was aware that one of the sites had been referred to OCI and that DSI was continuing to evaluate the field observations from inspections of other 3014 study sites. He, therefore, concluded that it would not be productive to potentially jeopardize the ongoing work of DSI and OCI by publicizing the data integrity concerns at the Advisory Committee meeting.

In the e-mail at issue, the Office Director used a summary phrase to describe a sentiment informed by several considerations. Recognizing its summary nature, the Office Director explicitly invited the addressees in the e-mail to call him if they wanted to discuss the issue in more detail.

6. **Trade Press Attachment Issue:** Von Eschenbach testified that FDA had noted that the final decision regarding approval of each indication would be made after a review of the information and analyses requested in another approvable letter sent to Sanofi-aventis after the advisory committee meeting.

Allegation: False, says Ross, because this letter asked for detailed data integrity information but there is no record FDA ever reviewed it.

Response: FDA's testimony on this issue is accurate. Dr. Von Eschenbach stated correctly that in the January 23, 2003 second approvable letter, "FDA noted that the final decision would be made after a review of the information and analyses sent in response to the second approvable letter." This paraphrase of what the second approvable letter states would be accurate, even if, as the trade press attachment implies, FDA had never reviewed the information and analyses submitted in response to the letter. However, to the extent that the trade press attachment is meant to allege that FDA never reviewed the sponsor's response to the second approvable letter, this allegation is incorrect.

Because Study 3014 was in question, rather than sending an approval letter, FDA sent an approvable letter to Sanofi-Aventis on January 24, 2003 that, among other things, asked the

company to address several unresolved issues, including the data integrity concerns in Study 3014. In Question 1.A.1 of FDA's January 24, 2003, Approvable Letter, FDA requested information on quality assurance audits or monitoring visits conducted by Sanofi-Aventis or any contract research organization (CRO) on sites conducting Study 3014. Sanofi-Aventis submitted responsive information to FDA on October 17, 2003. Thereafter, the review division asked DSI to assess the adequacy of the monitoring program of the sponsor/CRO by reviewing and comparing the information submitted by Sanofi-Aventis on October 17, 2003 with the FDA inspectional observations for the eight high enrolling sites.

DSI compared the data integrity information on Study 3014 submitted by the applicant with information DSI had from its own investigations. Based on observations of non-compliance with FDA regulations and evidence of fraud detected at four of the eight high enrolling sites that FDA inspected, DSI recommended that data from these four sites be excluded from consideration in the New Drug Application. Data from a fifth site was considered highly suspect because the clinical investigator was on probation from his State Medical Board. DSI found that the sponsor/CRO failed to detect significant problems later detected during the FDA inspections, calling into question the utility of sponsor monitoring to detect data integrity problems during the course of the study. For this reason, DSI concluded that the data from Study 3014 could not be relied upon to support approval because the integrity of data from all sites involved in Study 3014 could not be assured with any degree of confidence. DSI based this conclusion on its inspections and its review of relevant portions of the applicant's response to the January 24, 2003, approvable letter.

- 7. Trade Press Attachment Issue: Von Eschenbach repeated later in his testimony that Study 3014 was dropped for consideration in making the decision to approve Ketek.**

Allegation: This was contradicted by Kweder's email.

Response: FDA's testimony on this issue is accurate. This is the same assertion set forth in allegation #2 (above). Accordingly, please see our prior response.

- 8. Trade Press Attachment Issue: Von Eschenbach said limitations, such as under-reporting, were taken into account in assessing the data derived from foreign post-marketing experience reports.**

Allegation: Ross says the medical officer did not take them into account because their quality was too poor — he "simply ignored the problems."

Response: FDA's testimony on this issue is accurate. The medical officer did not "simply ignore the problems." On the contrary, in his review, the medical officer discusses the potential limitations associated with postmarketing experience thoroughly, citing references on the reliability of postmarketing data. This review document is the official FDA record of the primary medical officer's assessment of the postmarketing safety data for the Ketek NDA. FDA managers relied upon it as an integral part of the decision to approve Ketek, and it is publicly available as part of FDA's summary basis of approval for the Ketek NDA. The medical officer

concluded that substantial evidence of safety has been provided and recommended approval of Ketek.

The following is an excerpt from this medical officer's review:

There are many limitations of post-marketing adverse event reporting that apply when attempting to assess the potential hepatotoxicity of a particular drug. Capture of events in a passive-reporting post-marketing surveillance system is inefficient. A review article found that between 3% and 11% of hospital admissions could be attributed to adverse drug reactions.² However, another study suggests that as few as only 1% of all serious drug-related events are actually reported to the FDA.³ A recent study reported that in France, fewer than 6 percent of hepatic adverse drug reactions are ever reported.⁴

Further complicating assessment of post-marketing reports of hepatic adverse reactions is the finding that many such reports lack enough basic information to evaluate the possibility of a drug reaction. Also, many such post-marketing reports are likely to be unrelated to the incriminated drug as was found in a study in which, using international consensus criteria, only 47.1% of reported post-marketing hepatic adverse events were determined to be related to the drug in question.⁵

In addition, the very nature of idiosyncratic drug-induced hepatic adverse events is such that they are characterized by a variable delay, or latency period, which may range from 5-90 days after the initial ingestion of the drug. This may result in difficulty for the treating physician in assessing possible causality of a drug.

It is quite possible that the cases reviewed here represent a very small percentage of the overall number of telithromycin-associated post-marketing hepatic adverse events. And, when considering that a significant proportion of the limited post-marketing hepatic adverse events in this database either lack sufficient basic information or may even be unrelated to telithromycin exposure, it is difficult to make definite determinations of causality, incidence, and severity of reported hepatotoxic reactions.

However, past experience has shown with other drugs (such as bromfenac, troglitazone, and trovafloxacin) that despite this system's deficiencies, severe drug-related postmarketing hepatic adverse events are likely to be identified particularly when drug exposure is large and hepatic events occurring in otherwise healthy individuals are severe. The post-marketing hepatic adverse events reviewed here were generated from an estimated usage of 3.7 million prescriptions in several countries. The majority of these prescriptions (2.2 million) were dispensed in France and Germany.

² Beard K. Adverse reactions as a cause of hospital admissions in the aged. *Drugs Aging*. 1992;2:356-367

³ Scott HD, Rosenbaum SE, Waters WJ, et al. Rhode Island physicians' recognition and reporting of adverse drug reactions. *R I Med J*. 1987;70:311-316

⁴ Sgro C, et al. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology* 2002; 36:451-5

⁵ Aithal GP, et al. *BMJ* 1999;319:1541-1541, 11 December.

9. **Trade Press Attachment Issue:** The commissioner's sworn testimony said that although "one case of liver failure that resulted in death was found, it was not clear that this represented a signal beyond what had been seen in the data available at the time of approval."

Allegation: False, says Ross, because "this was exactly the signal that reviewers had been concerned about during the review."

Response: FDA's testimony on this issue is accurate. FDA identified and analyzed this single case of liver failure that resulted in death in a review of the data received through March 11, 2005, after Ketek had been approved for about one year in the U.S. The Office of Drug Safety (currently the Office of Surveillance and Epidemiology) conducted the review, which concludes that "it appears the cases of visual and hepatic adverse events are consistent with those seen prior to approval in worldwide experience and as described in the current labeling." In other words, the official review concluded that the single case of liver toxicity at issue was consistent with the data that FDA had reviewed at the time of approval, and it did not appear to signal a new problem.

10. **Trade Press Attachment Issue:** Three cases of serious liver toxicity, including one death, were described by von Eschenbach as having been previously reported to FDA, "although in less detail, making conclusions about them difficult to reach until the published information was available."

Allegation: Ross says a 1/23/06 email from the medical officer responsible for Ketek said the reporting physician about these cases "gave an extremely detailed report to FDA; the company gave a very sparse report."

Response: This allegation is inaccurate. The January 23, 2006, e-mail referred to in the allegation discusses the level of detail in the physician's report to FDA about only one case -- the case involving a death. There is no specific mention in the January 23, 2006 e-mail of the other two cases of serious liver toxicity and level of detail reported.

Nevertheless, in reviewing the testimony to respond to this allegation, we have identified an inaccuracy that we would like to correct and clarify. Specifically, we believe the testimony needs further clarification to explain the role that the article in the *Annals of Internal Medicine* played in FDA's review of Ketek. The testimony incorrectly characterizes the level of detail of the reports as the key contribution of the *Annals* article. Rather, the testimony should have emphasized the importance of the article as a catalyst for the FDA to conduct its comprehensive review of the Ketek safety information earlier than planned.

The January 23, 2006 email referred to in the allegation references the death that was first reported to the agency in February of 2005. This death was carefully considered in the June 14, 2005 review that the Office of Drug Safety (ODS, now the Office of Surveillance and Epidemiology) conducted as part of the one year safety review of Ketek (see response to Allegation #9). After the data cutoff date of March 11, 2005 for the one year review, the two

additional serious non-fatal cases of liver toxicity described in the Annals article were reported to FDA, but FDA did not again fully assess the combined liver toxicity data at that time. After online publication of the Annals article on January 20, 2006, FDA initiated its two year review of Ketek safety information earlier than planned. The detail provided to FDA prior to the Annals article about the two non-fatal cases lacked some of the specific information provided in the Annals article (e.g., some additional clinical details, and histopathologic photomicrographs and gross pathologic photographs for one of the patients). In addition, after the online publication of the Annals article, Sanofi-Aventis submitted follow-up reports on each of the three cases based on the Annals publication and one of the authors of the Annals article submitted reports on two of the cases directly to FDA that MedWatch staff received on January 25, 2006. (See table below).

Therefore, although FDA previously had received information about all three of these liver toxicity cases prior to the online publication of the Annals article, the agency conducted a thorough analysis of the available liver toxicity information once the online Annals article became available. Although it is true that the reports submitted to FDA prior to the online publication of the Annals article had somewhat less detail than those in the Annals article, upon recent reflection and in preparing the reply to this letter, FDA now believes that the reports did contain enough information for evaluation of the individual cases. The Annals article provided a catalyst for this comprehensive FDA review which enabled the agency to reach the conclusions it did earlier than it otherwise would have had it conducted its normal two year review. As discussed in the testimony, after assessing the complexities of all available information, on June 29, 2006, FDA announced the results of the review to the public and a new bolded warning about liver toxicity was added to Ketek's label.

Reports of Cases Presented in the Annals' Article		
Annals' Case #	Date Received by FDA	
	Direct Reports ¹	Manufacturer's Reports ¹
1 46 year-old White man	9-13-05	7-28-05
	1-25-06**	2-2-06**
2 51 year-old White woman	1-25-06**	4-29-05
		5-11-05
		8-8-05
		9-12-05
		11-17-05
		12-20-05
		1-31-06**
3 26 year-old Hispanic man	2-11-05	5-10-05
		2-2-06**

*Ann Intern Med. 2006;144:415-420.

**After the Annals publication.

¹A Direct Report is a report sent directly by healthcare professionals and consumers to FDA via MedWatch, the FDA Safety Information and Adverse Event Reporting Program. MedWatch allows healthcare professionals and

consumers to report serious problems that they suspect are associated with the drugs and medical devices they prescribe, dispense, or use.

²Manufacturers submit initial reports of adverse experiences, and follow-up reports for serious and unexpected adverse experiences when they receive new information or as requested by FDA (see 21 CFR 314.80(c)).

11. Trade Press Attachment Issue: Von Eschenbach testified “On February 12, 2007, FDA acted on the recommendations of the joint panel and announced revisions to the labeling and indications for Ketek designed to improve the safe use of Ketek by patients.”

Allegation: This, Ross says, was false because FDA “failed to institute the panel’s recommendation that visual adverse events receive a black box warning.”

Response: FDA’s testimony on this issue is accurate. On February 12, 2007, FDA did take actions based upon the recommendations of the joint panel. FDA followed the Advisory Committee’s advice with respect to labeling revisions and a change in Ketek’s approved indications. The Advisory Committee voted that a black box warning be included in the Ketek labeling, and the agency followed that recommendation. But the panel did not specifically recommend that the risk of visual adverse events be the subject of a black box warning.

After a close vote against the inclusion of hepatotoxicity in the black box, the Advisory Committee began to vote on the issue of inclusion of visual adverse events in a boxed warning, but stopped before completing the vote. Although some committee members expressed support for inclusion of the visual adverse events in the black box warning, other committee members were not in support of such an action and no formal vote on this recommendation was completed. Instead, the committee asked that FDA consider its deliberations as it made the final decisions regarding the revised labeling.

After the Advisory Committee meeting, FDA approved the following labeling changes for Ketek:

- Two previously approved indications were removed from the label (acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*; and acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus*.)
- Ketek is now indicated only for the treatment of community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydomphila pneumoniae*, or *Mycoplasma pneumoniae*, for patients 18 years and older.
- The updated label includes a boxed warning and a contraindication stating that no one with myasthenia gravis should take Ketek.
- Warnings were strengthened for loss of consciousness, and visual disturbances.
- Warnings for hepatotoxicity had already been strengthened in June 2006. In the February 2007 labeling change, the text relating to hepatotoxicity in the

PRECAUTIONS section was combined with the hepatotoxicity warnings to make one combined statement in the WARNINGS section.

- A Medication Guide was added to the labeling.

That is, FDA made substantial changes to Ketek's label based on concerns discussed and expressed at the December 14 and 15, 2006 Advisory Committee meeting. Specifically, we note that FDA explicitly strengthened the warning for visual disturbances. In light of these changes, it is clear that FDA took into full account the Advisory Committee's discussion of these issues and its recommendations before taking action.

###

Having discussed each of the allegations in the trade press attachment, we believe we have demonstrated that each allegation is without merit. We hope that this further information and these clarifications are helpful to the Committee in appreciating FDA's careful review of the Ketek matter over a period of several years.

Attachment 3



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-0115

APR 11 2007

The Honorable Bart Stupak
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-0115

Dear Chairman Dingell and Chairman Stupak:

I write in follow-up to the Food and Drug Administration's (FDA or the Agency) April 4, 2007, response to your letter dated March 28, 2007, regarding my written testimony at the March 22, 2007, Subcommittee on Oversight and Investigations hearing entitled, "The Adequacy of FDA Efforts to Assure the Safety Efforts of the Drug Supply -- Part II."

A copy of the Agency's response is enclosed. In addition, the following documents are being provided to further support our response:

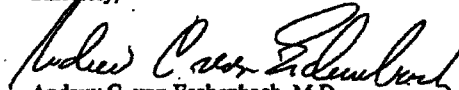
- December 14-15, 2006, Joint Meeting of the Anti-Infective Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, transcript, pages 301-426;
- 2003 Approvable Letter for Application NDA 21-144;
- Medical Officer Safety Review of NDA 21-144: Telithromycin (Ketek); and
- 2005 Office of Drug Safety evaluation of the safety profile of Telithromycin.

Information contained in the enclosures may include information that is trade secret, commercial confidential or other information protected from disclosure to the public under the Freedom of Information Act (Title 5, United States Code [U.S.C.], 552), the Trade Secrets Act (18 U.S.C. 1905), the Privacy Act (5 U.S.C. 552a) and FDA regulations. The Committee should not publish or otherwise make public any such information. We would be glad to discuss with the Committee staff the protected status of specific information.

Page 2 - The Honorable John D. Dingell
The Honorable Bart Stupak

Please be assured that FDA takes our obligations to Congress very seriously. We appreciate the opportunity to provide further information to you. If you have further questions, please let us know.

Sincerely,

A handwritten signature in black ink, appearing to read "Andrew C. von Eschenbach". The signature is fluid and cursive, with a large initial "A" and a long, sweeping underline.

Andrew C. von Eschenbach, M.D.
Commissioner of Food and Drugs

Enclosures

Attachment 4



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515-6143

JUN 7 2007

The Honorable Bart Stupak
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

This is in response to your letter dated March 28, 2007, in which you requested information with regard to Food and Drug Administration (the Agency) Commissioner Andrew von Eschenbach's testimony before the Subcommittee on Oversight and Investigations on March 22, 2007. Specifically, you have requested documents prepared for or used in the preparation of Dr. von Eschenbach's testimony. Additionally, you have requested interviews by Committee staff of persons participating in the preparation of the testimony submitted on March 22, 2007.

On April 4, 2007, the Agency provided a detailed explanation and supporting documentation demonstrating the basis for the accuracy of the eleven items that the Committee raised regarding Dr. von Eschenbach's testimony and prepared statement. Also, while you have requested additional documentation and interviews, we believe that the Agency's April 4 response and the accommodations proposed below should resolve these issues.

The documentation you have requested constitutes confidential deliberative communications between Dr. von Eschenbach and Agency employees. Circulating materials related to preparation for testimony before Congress or interviewing Agency staff about their involvement in the preparation of the Commissioner for testimony before Congress would have a chilling effect on the open exchange of views that is essential to the effective conduct of Agency business and would make it very difficult for advisors to provide full and frank advice to their colleagues. In an effort to accommodate the Committee's legitimate needs, while protecting the confidentiality of Executive Branch deliberations, we propose providing

Page 2 - The Honorable John D. Dingell
The Honorable Bart Stupak

a briefing to the Committee by Department staff regarding the concerns you have raised. In preparation for such a briefing, it would be most helpful for the Committee to identify its particular concerns regarding the response already provided.

I am hopeful that this proposed accommodation will provide the Committee with the information it legitimately needs, while at the same time respecting and preserving the critical Executive Branch interests at stake.

Sincerely,

A handwritten signature in cursive script that reads "Susan C. Winckler".

Susan Winckler
Acting Chief of Staff

Attachment 5

SUBPOENA

**BY AUTHORITY OF THE HOUSE OF REPRESENTATIVES OF THE
CONGRESS OF THE UNITED STATES OF AMERICA**

To Hon. Michael Leavitt, Secretary of Health and Human Services SERVE: Casey Hernard

You are hereby commanded to be and appear before the Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
of the House of Representatives of the United States at the place, date and time specified below.

- ☐ to testify touching matters of inquiry committed to said committee or subcommittee; and you are not to depart without leave of said committee or subcommittee.

Place of testimony: _____
Date: _____ Time: _____

- ☒ to produce the things identified on the attached schedule touching matters of inquiry committed to said committee or subcommittee; and you are not to depart without leave of said committee or subcommittee.

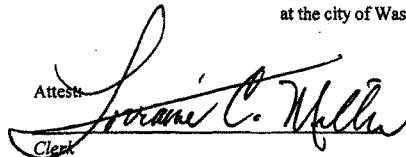
Place of production: 316 Ford House Office Building
Date: February 11, 2008 Time: 10:00 am

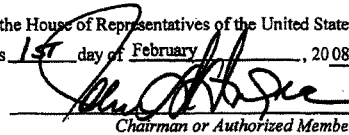
To U.S. Marshall or any authorized Committee staff member

_____ to serve and make return.

Witness my hand and the seal of the House of Representatives of the United States,
at the city of Washington, this 15 day of February, 2008.

Attest:


Clerk


Chairman or Authorized Member

PROOF OF SERVICESubpoena for Hon. Michael Leavitt, Secretary of Health and Human Services SERVE: Casey HemardAddress U.S. Department of Health and Human Services,200 Independence Avenue, S.W., Washington, D.C. 20201before the Committee on Energy and CommerceSubcommittee on Oversight and InvestigationsServed by (print name) David W. NelsonTitle Staff member - Committee on Energy + CommerceManner of service personal service to Casey HemardDate 2/1/02Signature of Server David W. NelsonAddress 316 Ford HDB - Washington, DC 20515

Schedule

In accordance with the attached schedule instructions, you are required to produce all records, in unredacted form, prepared for or used in the preparation of the testimony of the Commissioner of Food and Drugs, Andrew C. von Eschenbach, before the Committee on Energy and Commerce on March 22, 2007, by any employee of the Department of Health and Human Services (HHS), including, but not limited to—

- (A) any briefing books and background memoranda; and
- (B) all communications between and among senior staff of the Food and Drug Administration (FDA), the FDA Office of Legislative Affairs, the HHS Office of Legislative Affairs, and the HHS Office of General Counsel, including communications from the FDA Office of Chief Counsel to Commissioner von Eschenbach and his senior staff.

Schedule Instructions

1. In complying with this subpoena, you are required to produce all responsive records that are in your possession, custody, or control, whether held by you or your past or present agents, employees, and representatives acting on your behalf. You are also required to produce records that you have a legal right to obtain, that you have a right to copy or to which you have access, as well as records that you have placed in the temporary possession, custody, or control of any third party. No records called for by this request shall be destroyed, modified, removed, transferred or otherwise made inaccessible to the Committee or Subcommittee.
2. In the event that any entity, organization or individual denoted in this subpoena has been, or is also known by any other name than that herein denoted, the subpoena shall be read also to include them under that alternative identification.
3. Each record produced shall be produced in a form that renders the record capable of being copied.
4. Records produced in response to this subpoena shall be produced together with copies of file labels, dividers or identifying markers with which they were associated when this subpoena was served. Also identify to which paragraph from the subpoena such records are responsive.
5. It shall not be a basis for refusal to produce records that any other person or entity also possesses non-identical or identical copies of the same record.
6. If any of the subpoenaed information is available in machine-readable form (such as paper, magnetic tapes, drums, disks, or core storage), state the form in which it is available and provide sufficient detail to allow the information to be copied to a readable format. If the information requested is stored electronically, indicate whether you have an existing program that will print the records in a readable form.
7. If compliance with the subpoena cannot be made in full, compliance shall be made to the extent possible and shall include an explanation of why full compliance is not possible.
8. In the event that a record is withheld on the basis of privilege, provide the following information concerning any such record: (a) the privilege asserted; (b) the type of record; (c) the general subject matter; (d) the date, author and addressee; and (e) the relationship of the author and addressee to each other.
9. If any record responsive to this subpoena was, but no longer is, in your possession, custody, or control, identify the record (stating its date, author, subject and recipients) and explain the circumstances by which the record ceased to be in your possession, custody, or control.

10. If a date or other descriptive detail set forth in this subpoena referring to a record is inaccurate, but the actual date or other descriptive detail is known to you or is otherwise apparent from the context of the request, you should produce all records which would be responsive as if the date or other descriptive detail were correct.
11. The time period covered by this subpoena is included in the attached schedule(s).
12. This request is continuing in nature and applies to any newly-discovered information. Any record, compilation of data or information, not produced because it has not been located or discovered by the return date, shall be produced immediately upon location or discovery subsequent thereto.
13. All records shall be bates-stamped sequentially and produced sequentially.
14. The records shall be delivered to the Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, U.S. House of Representatives, 316 Ford House Office Building.

Definitions for Schedule

1. The term "records" shall be construed in the broadest sense and shall mean any written or graphic material, however produced or reproduced, of any kind or description, consisting of the original and any non-identical copy (whether different from the original because of notes made on or attached to such copy or otherwise) and drafts and both sides thereof, whether printed or recorded electronically or magnetically or stored in any type of data bank, including, but not limited to, the following: correspondence, memoranda, records, summaries of personal conversations or interviews, minutes or records of meetings or conferences, opinions or reports of consultants, projections, statistical statements, drafts, contracts, agreements, purchase orders, invoices, confirmations, telegraphs, telexes, agendas, books, notes, pamphlets, periodicals, reports, studies, evaluations, opinions, logs, diaries, desk calendars, appointment books, tape recordings, video recordings, e-mails, voice mails, computer tapes, or other computer stored matter, magnetic tapes, microfilm, microfiche, all other records kept by electronic, photographic, or mechanical means, charts, photographs, notebooks, drawings, plans, inter-office communications, intra-office and intra-departmental communications, transcripts, checks and canceled checks, bank statements, ledgers, books, records or statements of accounts, and papers and things similar to any of the foregoing, however denominated.
2. The terms "relating," "relate," or "regarding" as to any given subject means anything that constitutes, contains, embodies, identifies, deals with, or is in any manner whatsoever pertinent to that subject, including but not limited to records concerning the preparation of other records.
3. The term "communication" means each manner or means of disclosure or exchange of information, regardless of means utilized, whether oral, electronic, by document or otherwise, and whether face-to-face, in a meeting, by telephone, mail, telexes, discussions, releases, personal delivery, or otherwise.
4. The terms "and" and "or" shall be construed broadly and either conjunctively or disjunctively to bring within the scope of this subpoena any information which might otherwise be construed to be outside its scope. The singular includes plural number, and vice versa. The masculine includes the feminine and neuter genders.
5. The terms "person" or "persons" means natural persons, firms, partnerships, associations, corporations, subsidiaries, divisions, departments, joint ventures, proprietorships, syndicates, or other legal, business or government entities, and all subsidiaries, affiliates, divisions, departments, branches, and other units thereof.
6. The term "identify," when used in a question about individuals, means provide the following information: (a) the individual's complete name and title; and (b) the individual's business address and phone number

Attachment 6



U.S. Department of Justice
Office of Legislative Affairs

Office of the Assistant Attorney General

Washington, D.C. 20530

January 27, 2000

The Honorable John Linder
Chairman, Subcommittee on Rules and
Organization of the House
Committee on Rules
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

We have carefully reviewed the testimony presented to the Subcommittee on Rules and Organization of the House at its hearing on July 15, 1999; on "Cooperation, Comity, and Confrontation: Congressional Oversight of the Executive Branch." The Department of Justice appreciates the Subcommittee's interest in this area, and we would like to take this opportunity to present in this letter, for the benefit of both Members of Congress and the public at large, the approach we take to the issues raised at the hearing. As always, we are committed to cooperating with your Subcommittee, and all committees of Congress, with respect to the oversight process.

The testimony presented at the hearing suggests to us that there is a need for improved communication and sensitivity between the Executive and Legislative Branches regarding our respective institutional needs and interests. It also suggests that there is considerable misunderstanding about the principles that govern the Department's longstanding positions and practices on responding to congressional oversight requests. We hope that this discussion of those governing principles will be helpful to the Committee and foster an improved understanding of the Department's interests in responding to oversight requests.

General Approach

The oversight process is, of course, an important underpinning of the legislative process. Congressional committees need to gather information about how statutes are applied and funds are spent so that they can assess whether additional legislation is necessary either to rectify practical problems in current law or to address problems not covered by current law. By helping Congress be better informed when it makes legislative decisions, oversight promotes the accountability of government. The information that committees gather in this oversight capacity is also important for the Executive Branch in the future implementation of the law and its participation in the legislative process. We have found that the oversight process can shed

valuable light on Department operations and assist our leadership in addressing problems that might not otherwise have been clear.

President Reagan's November 4, 1982 Memorandum for the Heads of Executive Departments and Agencies on "Procedures Governing Responses to Congressional Requests for Information" sets forth the longstanding Executive Branch policy on cooperating with Congressional oversight:

The policy of this Administration is to comply with Congressional requests for information to the fullest extent consistent with the constitutional and statutory obligations of the Executive Branch . . . [E]xecutive privilege will be asserted only in the most compelling circumstances, and only after careful review demonstrates that assertion of the privilege is necessary. Historically, good faith negotiations between Congress and the Executive Branch have minimized the need for invoking executive privilege, and this tradition of accommodation should continue as the primary means of resolving conflicts between the Branches.

The D.C. Circuit Court of Appeals has recognized the obligations of Congress and the Executive Branch to seek to accommodate the legitimate needs of the other:

The framers . . . expect[ed] that where conflicts in scope of authority arose between the coordinate branches, a spirit of dynamic compromise would promote resolution of the dispute in the manner most likely to result in efficient and effective functioning of our governmental system. Under this view, the coordinate branches do not exist in an exclusively adversary relationship to one another when a conflict in authority arises. Rather, each branch should take cognizance of an implicit constitutional mandate to seek optimal accommodation through a realistic evaluation of the needs of the conflicting branches in the particular fact situation.

United States v. American Tel. & Tel. Co., 567 F.2d 121, 127 (D.C. Cir. 1977). Attorney General William French Smith captured the essence of the accommodation process in a 1981 opinion: "The accommodation required is not simply an exchange of concessions or a test of political strength. It is an obligation of each branch to make a principled effort to acknowledge, and if possible to meet, the legitimate needs of the other branch." Opinion of the Attorney General for the President, Assertion of Executive Privilege in Response to a Congressional Subpoena, 5 Op. O.L.C. 27, 31 (1981).

In implementing the longstanding policy of the Executive Branch to comply with Congressional requests for information to the fullest extent consistent with the constitutional and statutory obligations of the Executive Branch, the Department's goal in all cases is to satisfy legitimate legislative interests while protecting Executive Branch confidentiality interests. Examples of confidential information include national security information, materials that are

protected by law (such as grand jury information pursuant to Rule 6(e) of the Federal Rules of Criminal Procedure and taxpayer information pursuant to 26 U.S.C. § 6103); information the disclosure of which might compromise open criminal investigations or prosecutions or civil cases or constitute an unwarranted invasion of personal privacy; and predecisional deliberative communications (such as internal advice and preliminary positions and recommendations).

We believe that it must be the Department's efforts to safeguard these important Executive Branch institutional interests that have led to the frustrations expressed during the Subcommittee's hearing. We hope that we can reduce those frustrations in the future by setting forth here our perspective on some of the more important institutional interests that are implicated during the course of Congressional oversight.

Open Matters

Much of the testimony at the hearing addressed oversight of ongoing Department investigations and litigation. Although Congress has a clearly legitimate interest in determining how the Department enforces statutes, Congressional inquiries during the pendency of a matter pose an inherent threat to the integrity of the Department's law enforcement and litigation functions. Such inquiries inescapably create the risk that the public and the courts will perceive undue political and Congressional influence over law enforcement and litigation decisions. Such inquiries also often seek records and other information that our responsibilities for these matters preclude us from disclosing. Consequently, we have sought whenever possible to provide information about closed, rather than open, matters. This enables Congress to analyze and evaluate how statutory programs are handled and the Department conducts its business, while avoiding the potential interference that inquiries into open matters entail.

The open matters concern is especially significant with respect to ongoing law enforcement investigations. The Department's longstanding policy is to decline to provide Congressional committees with access to open law enforcement files. Almost 60 years ago, Attorney General Robert H. Jackson informed Congress that:

It is the position of the Department, restated now with the approval of and at the direction of the President, that all investigative reports are confidential documents of the executive department of the Government, to aid in the duty laid upon the President by the Constitution to "take care that the Laws be faithfully executed," and that congressional or public access to them would not be in the public interest

40 Op. Att'y. Gen. 45, 46 (1941). Attorney General Jackson's position was not new. His letter cited prior Attorney General letters taking the same position dating back to the beginning of the 20th century (*id.* at 47-48).

The rationale for this policy is set forth in a published opinion of the Office of Legal Counsel issued by Charles J. Cooper, Assistant Attorney General for the Office of Legal Counsel

during part of the Reagan Administration. See Response to Congressional Requests for Information Regarding Decisions made Under the Independent Counsel Act, 10 Op. O.L.C. 68, 76-77 (1986). Mr. Cooper noted that providing a Congressional committee with confidential information about active criminal investigations would place the Congress in a position to exert pressure or attempt to influence the prosecution of criminal cases. Id. at 76. Congress would become, "in a sense, a partner in the investigation," id., and could thereby attempt to second-guess tactical and strategic decisions, question witness interview schedules, debate conflicting internal recommendations, and generally attempt to influence the outcome of the criminal investigation. Such a practice would significantly damage law enforcement efforts and shake public and judicial confidence in the criminal justice system. Id. at 76-77.

Decisions about the course of an investigation must be made without reference to political considerations. As one Justice Department official noted 30 years ago, "the Executive cannot effectively investigate if Congress is, in a sense, a partner in the investigation. If a congressional committee is fully apprised of all details of an investigation as the investigation proceeds, there is a substantial danger that congressional pressures will influence the course of the investigation." Memorandum for Edward L. Morgan, Deputy Counsel to the President, from Thomas E. Kauper, Deputy Assistant Attorney General, Office of Legal Counsel, Re: Submission of Open CID Investigation Files 2 (Dec. 19, 1969).

In addition to the problem of Congressional pressure and the appearance of such pressure, the disclosure of documents from our open files could also provide a "road map" of the Department's ongoing investigations. The documents, or information that they contain, could come into the possession of the targets of the investigation through inadvertence or a deliberate act on the part of someone having access to them. The investigation would be seriously prejudiced by the revelation of the direction of the investigation, information about the evidence that the prosecutors have obtained, and assessments of the strengths and weaknesses of various aspects of the investigation. As Attorney General Jackson observed:

Disclosure of the [law enforcement] reports could not do otherwise than seriously prejudice law enforcement. Counsel for a defendant or a prospective defendant, could have no greater help than to know how much or how little information the Government has, and what witnesses or sources of information it can rely upon. This is exactly what these reports are intended to contain.

40 Op. Atty. Gen. at 46. The Department has similar interests in the confidentiality of internal documents relating to its representation of the United States in civil litigation. Our litigation files usually contain confidential correspondence with client agencies as well as the work product of our attorneys in suits that frequently seek millions of tax dollars. They also contain "road maps" of our litigation plans and preparations, as well as confidential reports from experts and consultants. Those plans could be seriously jeopardized and our positions in litigation compromised if we are obliged to disclose our internal deliberations including, but not limited to,

our assessments of the strengths and weaknesses of evidence or the law, before they are presented in court. That may result in an unfair advantage to those who seek public funds and deprive the taxpayers of confidential representation enjoyed by other litigants.

In addition, the reputations of individuals mentioned in internal law enforcement and litigation documents could be severely damaged by the public release of information about them, even though the case might ultimately not warrant prosecution or other legal action. The Department takes very seriously its responsibility to respect the privacy interests of individuals about whom information is developed during the law enforcement process or litigation.

Internal Department Deliberations

With respect to oversight on closed matters, the Department has a broad confidentiality interest in materials that reflect its internal deliberative process. In particular, we have sought to ensure that all law enforcement and litigation decisions are products of open, frank and independent assessments of the pertinent law and facts -- uninhibited by political and improper influences that may be present outside the Department. We have long been concerned about the chilling effect that would ripple throughout government if prosecutors, policy advisors at all levels and line attorneys believed that their honest opinion -- be it "good" or "bad" -- may be the topic of debate in Congressional hearings or floor debates. These include assessments of evidence and law, candid advice on strengths and weaknesses of legal arguments, and recommendations to take or not to take legal action against individuals and corporate entities.

The Department must seek to protect this give-and-take process so that the participants in the process can vigorously debate issues before them and remain able to provide decisionmakers with complete and honest counsel regarding the conduct of the Department's business. If each participant's contribution can be dissected by Congress in a public forum, then the free and candid flow of ideas and recommendations would certainly be jeopardized. The Supreme Court has recognized the legitimacy of this "chilling effect" concern: "Human experience teaches that those who expect public dissemination of their remarks may well temper candor with a concern for appearances and for their own interests to the detriment of the decisionmaking process." United States v. Nixon, 418 U.S. 683, 705 (1974). Our experience indicates that the Department can develop accommodations with Congressional committees that satisfy their needs for information that may be contained in deliberative material while at the same time protecting the Department's interest in avoiding a chill on the candor of future deliberations.

The foregoing concerns apply with special force to Congressional requests for prosecution and declination memoranda and similar documents. These are extremely sensitive law enforcement materials. The Department's attorneys are asked to render unbiased, professional judgments about the merits of potential criminal and civil law enforcement cases. If their deliberative documents were made subject to Congressional challenge and scrutiny, we would face a grave danger that they would be chilled from providing the candid and independent analysis essential to just and effective law enforcement or, just as troubling, that

they might err on the side of prosecution simply to avoid public second-guessing. This in turn would undermine public and judicial confidence in our law enforcement processes, untoward consequences we are confident that Congress, like the Department, wishes to avoid.

Privacy

In addition to these concerns, disclosure of declination memoranda would implicate significant individual privacy interests as well. Such documents discuss the possibility of bringing charges against individuals who are investigated but not prosecuted, and often contain unflattering personal information as well as assessments of witness credibility and legal positions. The disclosure of the contents of these documents could be devastating to the individuals they discuss. We try to accommodate Congressional needs for information about declinations whenever possible by making appropriate Department officials available to brief Committee Members and staff. This affords us an opportunity to answer their questions, which can be helpful because it can include the context and process that accompanied the decision. Hence, the discussion with staff may provide useful information and minimize the intrusion on individual privacy and the chill on our attorneys' preparation of future deliberative documents.

Line Attorneys

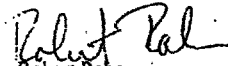
The Department also has a strong institutional interest in ensuring that appropriate supervisory personnel, rather than line attorneys and agents, answer Congressional questions about Department actions. This is based in part upon our view that supervisory personnel, not line employees, make the decisions that are the subjects of congressional review, and therefore they should be the ones to explain the decisions. More fundamentally, however, we need to ensure that our attorneys and agents can exercise the independent judgment essential to the integrity of law enforcement and litigation functions and to public confidence in those decisions. Senator Orrin Hatch has recognized the legitimacy of the Department's practice in this area, observing that Congressional examination of line attorneys "could chill career Department of Justice lawyers in the exercise of their daily duties." See Letter to Attorney General Janet Reno from Senator Orrin Hatch, dated September 21, 1993. Representative Henry Hyde has likewise opposed Congressional interviews of line prosecutors. See Letter of Representative Hyde to Representative Carlos Moorhead, dated September 7, 1993. By questioning supervisors and ultimately the Department's Senate-confirmed leadership, Congress can fulfill its oversight responsibilities without undermining the independence of line attorneys and agents.

* * *

In sum, the Department recognizes that the process of Congressional oversight is an important part of our system of government. We are committed to cooperating with oversight requests to the fullest extent consistent with our constitutional and statutory responsibilities.

We welcome your suggestions about how we should work together to accommodate the needs of our respective branches of government. Please do not hesitate to contact me if you would like to discuss these matters further. I intend at all times to work diligently with you toward satisfying the respective needs of our coordinate branches.

Sincerely,


Robert Raben
Assistant Attorney General

cc: The Honorable Tony Hall
Ranking Minority Member

United States Senate

COMMITTEE ON FINANCE
WASHINGTON, DC 20510-6200

February 6, 2008

Via Electronic Transmission

The Honorable Michael O. Leavitt
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

The Honorable Andrew C. von Eschenbach M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Secretary Leavitt and Commissioner von Eschenbach:

As a senior member of the United States Senate and as Ranking Member of the Committee on Finance (Committee), it is my duty under the Constitution to conduct oversight into the actions of the executive branch, including the activities at the Food and Drug Administration (FDA/Agency), a part of the Department of Health and Human Services (HHS). Previously, I wrote to Dr. von Eschenbach and his predecessor, Dr. Lester Crawford, regarding troubling allegations that a pharmaceutical company attempted to discredit the findings of Dr. Victoria Hampshire, an Agency employee and commissioned officer in the Public Health Service (PHS).

This Letter is based upon a comprehensive review of thousands of pages of documents obtained by my Committee staff. Portions of these documents were received by the Committee in response to letter requests to FDA, Wyeth Pharmaceuticals (Wyeth), its subsidiary division Fort Dodge Animal Health (FDAH), and Germinder and Associates, Inc. (GAI)—a public relations firm.¹ Wyeth hired GAI to handle public relations regarding its canine drug ProHeart 6. ProHeart 6 is a Wyeth Pharmaceuticals product designed to prevent canine heartworm and to treat both the larval and adult stages of the canine hookworm.² Additionally, this Letter contains information obtained by my Committee staff through interviews conducted with, among others, representatives of the aforementioned parties.

I. Background

On April 11, 2005, Committee staff received allegations from Dr. Victoria Hampshire that on January 7, 2005, she was wrongfully removed from her post at the Food and Drug

¹ Documents marked with Bates numbers beginning with the letters "FTDO" are documents obtained from Wyeth. Documents marked with Bates numbers beginning with letters "GA" came from Germinder and Associates. Please see the attached Appendix for descriptions of the cited documents.

² ProHeart 6 (moxidectin) background document, Fort Dodge Animal Health Presentation, January 2005, available at <http://www.fda.gov/cvm/Documents/FINALVMAProHeart6.pdf> (Attachment (Att.) 3).

Administration's Center for Veterinary Medicine (CVM) and was reassigned to another position.³

Dr. Hampshire informed Committee staff that she believed that she was removed and reassigned because of her work cataloging negative adverse drug events (ADEs) in conjunction with ProHeart 6. Her work demonstrated that the ProHeart 6 ADEs were increasing in frequency and in severity of associated safety signals. The ADE reports were sent to FDA from Fort Dodge Animal Health under the sponsor's mandatory reporting requirement and referred by Dr. Hampshire to her supervisors.⁴ Dr. Hampshire believes that she was removed at the behest of Wyeth in an effort to minimize the impact of a presentation she was going to make at a Veterinary Medicine Advisory Committee (VMAC) meeting regarding her findings.⁵ In 2005, I opened an inquiry into these allegations regarding ProHeart 6, issued document requests, and my staff began conducting interviews.

My staff has uncovered evidence supporting Dr. Hampshire's allegations, bringing into question the processes that FDA uses in response to industry allegations of wrongdoing by FDA employees. Their findings, as set out below, indicate that an industry sponsor may have used its resources to have the Adverse Events Coordinator removed in hopes of having its veterinary drug, ProHeart 6, returned to the market. Dr. Hampshire has offered credible evidence that the allegations Wyeth made against her to the FDA were misleading and easily refuted. Nonetheless, the FDA accepted Wyeth's allegations at face value and took actions against Dr. Hampshire that may have adversely affected the drug approval and recall processes. I offer the following findings and set forth a number of questions for the FDA.

A. Dr. Victoria Hampshire

The Committee obtained the following information about Dr. Hampshire through interviews, an April 11, 2005, letter she submitted to my staff, and documentation provided by various sources.

Dr. Victoria Hampshire, VMD, is a veterinarian and a Commander in the United States Public Health Service (PHS). In November 2003, Dr. Hampshire was promoted to Adverse Event Coordinator for CVM. This position required Dr. Hampshire to interact with pet owners whose animals were harmed and/or injured by products that are regulated by FDA through CVM. Among her major duties was the collection and analysis of thousands of adverse drug event reports. Dr. Hampshire's exemplary work at the FDA earned her a PHS Achievement Medal in June 2005 for her "significant achievements in post marketing veterinary drug surveillance."⁶ Moreover, she was named Veterinarian of the Year in 2006 by the PHS.⁷

³ Letter from Dr. Victoria Hampshire to Senate Finance Committee, April 11, 2005, with redactions (Att. 1).

⁴ 21 CFR 514.80 requires companies to report veterinary or owner reports of suspect adverse drug experiences and product/manufacturing defects on Form FDA 1932, "Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report."

⁵ Letter from Dr. Victoria Hampshire to Senate Finance Committee, April 11, 2005 (Att. 1).

⁶ Nomination for US PHS Achievement Medal CDR Victoria Hampshire (Att. 51).

Prior to joining the FDA in May 2001 as a Safety Reviewer, Dr. Hampshire worked at the National Institutes of Health (NIH) until 1999 and worked independently as a veterinarian for one year. During Dr. Hampshire's time as an independent veterinarian in 2000, she formed a company called Advanced Veterinary Applications (AVA). AVA operated through an internet website as a vehicle for providing veterinary services limited to friends, family, and former clients. The website accommodated house calls, relief work, and/or the prescribing of veterinary medications for a limited number of clients including friends, relatives, and colleagues. AVA was not an internet pharmacy. The website had an affiliation with VetCentric, an independent third party prescription fulfillment house that fills orders generated by the website. This method is commonly used by veterinarians who have few clients or practice on a limited basis.

VetCentric prescribing accounts allow veterinarians to save on overhead and generate income by marking up prescriptions with a margin. In Dr. Hampshire's case, her margin was a maximum of \$5.00 to cover her time spent. In many instances, she charged nothing at all. Thus, her website generated minimal income and was not designed to solicit general internet clients.⁸ Over a period of three years, from 2003 until 2005, Dr. Hampshire told Committee investigators that she received approximately \$200 as a result of the AVA website (but see fn. 154, below). Dr. Hampshire viewed this site as one of three outside activities she was allowed to undertake while employed at FDA.

Dr. Hampshire filed disclosures for AVA during her employment with FDA.⁹ In addition to AVA, Dr. Hampshire also disclosed two other outside activities, including limited employment at an emergency animal clinic and consultation work with the Humane Society of the United States. Dr. Hampshire also filed disclosures for other outside interests including speeches and talks that she gave outside of the Agency. All of these activities occurred outside of the scope of her government work and did not involve the use of FDA resources.

B. ProHeart 6 and Wyeth Pharmaceuticals

ProHeart 6, also known as moxidectin, is a Wyeth Pharmaceuticals product designed to treat both the larval and adult stages of the canine hookworm.¹⁰ It is administered bi-annually with an injection at a veterinarian's office. ProHeart 6 was developed in part as a convenience to pet owners who want to protect their pets without using monthly pills or external creams and lotions. Further, the bi-annual injection was marketed as providing continuous protection against parasites.

⁷ See http://www.washingtonpost.com/wp-dyn/content/article/2006/05/11/AR2006051101883_2.html (Att. 52).

⁸ Dr. Hampshire informed us that she received so little income from VetCentric and so much "junk mail" that she often threw away the VetCentric correspondence, including checks from time to time.

⁹ See Att. 56 (Disclosure forms filed by Dr. Hampshire). Dr. Hampshire had no ownership interest in VetCentric, so filed no disclosures regarding that company.

¹⁰ ProHeart 6 (moxidectin) background document, Fort Dodge Animal Health Presentation, January 2005, available at <http://www.fda.gov/cvm/Documents/FINALVMACProHeart6.pdf> (Att. 3).

ProHeart 6 was approved for use in the United States by the FDA in June 2001, based on laboratory studies that revealed no serious adverse drug events in healthy dogs.¹¹ ProHeart 6 is approved in several other countries, and a newer twelve-month version known as ProHeart SR12 has been approved for use in Australia since 2000.

Beginning in 2001, CVM and FDAH began receiving ADE reports from pet owners and veterinarians across the country. Initially, it appeared that many of the ADEs involved allergic-type reactions after administration of the drug.¹² The reactions that were cataloged as allergic reactions were attributed by FDAH to a manufacturing issue. FDAH allegedly resolved and “continu[ed] to optimize the manufacturing process.”¹³

In the months following its approval, other problems plagued ProHeart 6. As a result, the label for ProHeart 6 was amended three separate times. The first amendment in June 2002 added anaphylaxis/anaphylactoid reactions, depression, lethargy, hives, and head and facial edema.¹⁴ The label was amended a second time in November 2002 to include cardiopulmonary issues associated with dogs that were heartworm-positive.¹⁵ Finally, the phrase “and rare reports of death” was added to the label in July 2003.¹⁶ In addition to the label changes, the FDA required FDAH to send out two “Dear Doctor” letters noting the new information on the labels—one in July 2002, the second in June 2003.¹⁷ As 2003 drew to a close, concerns began to arise among FDA safety reviewers about the increasing number of ADEs being reported by veterinarians and pet owners to both FDAH and CVM.

C. Removal of ProHeart 6 from the Market

In November 2003, Dr. Hampshire began noticing an increasing trend in ADEs being reported to CVM by FDAH, veterinarians, and pet owners across the country.¹⁸ She alerted both the project manager and the team leader about this trend and suggested that the FDA should take some action to control the adverse impact that ProHeart 6 appeared to have on dogs in the United States.¹⁹ Dr. Hampshire’s initial outreach to her colleagues was heard, but no action was taken; in fact, Dr. Hampshire recalls that one of her colleagues stated, “The drug [ProHeart 6] will go away on its own after enough animals die.”²⁰ However, this sentiment at the FDA changed in the spring of 2004 when consumer advocacy groups began to contact CVM en masse, lodging complaints about ProHeart 6.

¹¹ FDA Veterinary Medicine Advisory Committee (VMAC) Meeting, January 31, 2005, Testimony of Dr. Lynn Post (Att. 4).

¹² ProHeart 6 (moxidectin) background document (Att. 3).

¹³ *Id.* at p. 48.

¹⁴ FDA VMAC Meeting, January 31, 2005 (Att. 4).

¹⁵ *Id.*

¹⁶ *Id.* Testimony of Dr. Margarita Brown (Att. 4).

¹⁷ <http://www.fda.gov/cvm/Documents/proheart6.pdf> (Att. 47);

<http://www.fda.gov/cvm/Documents/Proheart6-062703.doc> (Att. 48).

¹⁸ Letter from Dr. Victoria Hampshire to Senate Finance Committee, dated April 11, 2005 (Att.1).

¹⁹ *Id.*

²⁰ *Id.*

Consumer groups continued to press the FDA through the spring of 2004 and ultimately generated over 20 national news stories regarding the various adverse reactions pets had with ProHeart 6.²¹ In response, FDA officials, including the head of the Office of New Drug Evaluation, began to ask when the FDA was going to act. FDA senior management, including the then-Director at CVM (Dr. Stephen F. Sundlof),²² then-Deputy Director at CVM (Dr. Linda Tollefson), and the head of the Office of Surveillance and Compliance (OSC) (Dr. Dan McChesney), agreed to hear a presentation provided by Dr. Hampshire about the safety issues associated with the adverse drug event reports that CVM received. Dr. Hampshire made her presentation in July 2004. According to Dr. Hampshire, the CVM senior management staff unanimously agreed that ProHeart 6 was problematic and that it should be removed from the market, and that Wyeth should be asked to conduct additional studies.²³ In making this decision, Agency staff relied upon the nearly 5,000 ADE reports that were relayed to the FDA and the fact that there were large numbers of reports on relatively young, healthy dogs.²⁴

Dr. Sundlof took the concerns that the management team raised and notified then-FDA Commissioner, Dr. Lester Crawford, who is also a veterinarian. According to Dr. Hampshire, Dr. Crawford asked Dr. Sundlof to speed up the process on ProHeart 6 in anticipation of the upcoming heartworm season and the potential increase in utilization. FDA officials at CVM scheduled a meeting with Wyeth officials to discuss concerns surrounding ProHeart 6. On August 11, 2004, FDA officials from CVM met with representatives of FDAH, a Wyeth subsidiary, to review the same presentation Dr. Hampshire gave to CVM management in July. Dr. Hampshire told Committee staff that she was unable to attend the August meeting. A follow-up meeting was set for September 1.

Dr. Hampshire stated that she represented CVM at the September 1 meeting and presented the findings, which were supported by seven safety reviewers, as well as CVM management.²⁵ By the end of the meeting, CVM decided that it would ask FDAH to remove ProHeart 6 from the market.

Following the September 1, 2004, meeting, FDAH continued to appeal the decision of CVM senior management to FDA's then-Commissioner Crawford.²⁶ The appeal included arguments that the data was inconclusive and that other competitor heartworm products had similar adverse events.²⁷ CVM staff, including Dr. Hampshire, advised the FDA Commissioner that this comparison had been addressed previously by changes to dosage and new warnings on other competitor drugs.²⁸ The then-FDA Commissioner Crawford ultimately concluded that CVM's decision was fair and accurate and the FDA proceeded with the recall.²⁹ FDAH made one last appeal to the FDA Chief Counsel who

²¹ See, e.g., <http://www.dogsadversereactions.com> (moxidectin link).

²² Dr. Sundlof is now the Director of FDA's Center for Food Safety and Applied Nutrition (CFSAN).

²³ Letter from Dr. Hampshire to Senate Finance Committee, April 11, 2005 (Att. 1).

²⁴ See FDA VMAC Meeting, January 31, 2005, Testimony of Dr. Margarita Brown, pp. 16 and 34-52. Dr. Brown was one of four veterinarians who initially reviewed adverse drug events for CVM. She synthesized why the adverse reports were serious (Att. 4).

²⁵ Letter from Dr. Hampshire to Senate Finance Committee, April 11, 2005 (Att. 1).

²⁶ *Id.*

²⁷ *Id.*

²⁸ *Id.*

²⁹ *Id.*

also rejected the appeal and upheld the recall.³⁰ Finally, on September 3, 2004, FDAH voluntarily recalled ProHeart 6 from the market,³¹ provided that CVM would convene an outside panel of experts to reevaluate the data.

II. Findings

Set forth below are my Committee staff's findings with regard to ProHeart 6 and Dr. Hampshire.

A. Wyeth Pharmaceuticals' Investigation of Dr. Victoria Hampshire

1. Initial Disputes with FDA and Dr. Hampshire

Internal emails from FDAH following the September 3, 2004, recall of ProHeart 6, show that it requested a copy of the September 2004 slide presentation prepared by Dr. Hampshire.³² Dr. Hampshire and CVM officials initially withheld the slide presentation because of particular concerns regarding the confidentiality of outside consultants that the FDA utilized in preparing the data. Dr. Hampshire believed the FDA needed the approval of the outside consultants before divulging their names to a drug sponsor because the use of the consultants was "pre-decisional."

On September 20, 2004, the President of FDAH, Dr. Thomas Corcoran, asked that Dr. Sundlof provide FDAH with the September 1 slide presentation.³³ Three days later, on September 23, 2004, Dr. Corcoran wrote a formal letter to Dr. Sundlof in which he continued to request the September slide presentation, asked for a narrative to accompany the slide presentation, and requested "the list of academics Dr. Hampshire consulted with in evaluating ProHeart 6."³⁴ On September 24, 2004, Dr. Sundlof responded to the Dr. Corcoran and provided a redacted copy of the September 1 slide presentation prepared by Dr. Hampshire. In the response, Dr. Sundlof stated, "[i]n considering your request for the names of the experts outside the Agency which Dr. Hampshire referred to during her presentation, CVM has determined that the information is pre-decisional and therefore considered confidential, thus we are declining to provide their names."³⁵

Internal FDAH emails indicate that Dr. Corcoran sought internal guidance from FDAH Corporate Counsel regarding the ability of CVM to withhold this information as "pre-decisional."³⁶ Based on these internal discussions, Dr. Corcoran continued to ask the then-CVM director for the unredacted slides. In an email dated October 4, 2004, Dr. Corcoran stated, "In going through the presentation [sic] slides were omitted. Would you look into this and let me know if the missing slides were omitted for a specific reason?"³⁷ Dr. Corcoran continued, "I need to understand the context of the 'predecisional' [sic]

³⁰ *Id.*

³¹ <http://www.fda.gov/cvrm/PH6QA.htm> (Att. 49).

³² FTDO 001391 (Att. 5).

³³ FTDO 000845 (Att. 6).

³⁴ FTDO 000846-848, at 847 (Att. 7).

³⁵ FTDO 00929 (Att. 7a).

³⁶ See FTDO 000845 (Att. 6).

³⁷ FTDO 001075 (Att. 10).

statement that guides you to withhold the information from whom in the academic world you received advice on ProHeart 6. Obviously the nature of the advice is also key.”³⁸ Finally, Dr. Corcoran commented on conversations with CVM, “The confrontational tone exhibited by some of the CVM personnel at the September 1 meeting seems to be continuing. Why?”³⁹

As a follow-up to the October 4 email, Dr. Corcoran called Dr. Sundlof the following day to discuss the September 1 slide presentation. Contemporaneous notes of the conversation prepared by Dr. Corcoran provide a narrative of the call. Specifically, Dr. Corcoran wrote:

On the issue of the “missing” slides from Dr. Hampshire’s September 1 presentation, Dr. Sundlof stated he was told we were given all slides with data. Slides with commentary and conclusions were omitted. I told him this was totally unacceptable. If CVM presented this information as factual and it was the basis of their decision to demand we voluntarily recall ProHeart 6, we had an absolute right to see the complete presentation and they had an obligation to provide. *I further told him that unless we received the entire presentation, I was going to make a big issue of initially withholding the presentation and then submitting only a portion of the presentation. I assured him this would be carried to the highest levels, and I wasn’t speaking of FDA. He stated, “Message received.”*⁴⁰ (emphasis added).

Following this conversation with FDAH’s president, Dr. Sundlof emailed an un-redacted version of the complete September 1 slide presentation to FDAH on October 7, 2004.⁴¹ In transmitting the slides, Dr. Sundlof noted, “The set I sent previously mostly omitted the conclusion slides because I thought, and still do think, that it is more important for FDAH to draw their own conclusion from the data in the reports FDAH sent to CVM rather than focusing on what FDAH considers problems with CVM’s conclusions.”⁴²

2. Initial Complaints about Dr. Hampshire

One week following the September 3, 2004, removal of ProHeart 6 from the market, evidence suggests that individuals at FDAH received concerns regarding the possibility that Dr. Hampshire had a “vendetta” against FDAH and ProHeart 6. On September 10, 2004, Dr. Rocky Bigbie, Director of Field Veterinary Services at FDAH, received an email from M. Gatz Riddell, Jr., then-professor at Auburn University, who stated, “I have also heard that Tori Hampshire might have been on a mission with some type of ax to grind or a vendetta to carry out.”⁴³

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ FTDO 001654 (Att. 11).

⁴¹ FTDO 001803 (Att. 12).

⁴² *Id.*

⁴³ FTDO 000878 (Att. 13). Dr. Riddell was a source of information to FDAH that Dr. Hampshire may have a personal “vendetta” against ProHeart 6, and he was also an “Invited, Voting Consultant” to the VMAC.

Further, that same day, a representative of the American Veterinary Medical Association forwarded an email from Larry Glickman, VMD, a professor at Purdue University, which discussed Dr. Hampshire.⁴⁴ The email concluded that Dr. Hampshire's actions were important because they "reflect[] a deliberate attempt by Victoria Hampshire to exclude veterinarians in the decision making process."⁴⁵

3. Hiring Consultants to Investigate Dr. Hampshire

During September 2004, FDAH began an effort to get ProHeart 6 back on the market. Disclosures made to Committee staff indicate that on September 5, 2004, FDAH Director of Marketing Craig Wallace contacted Lea Ann Germinder of Germinder & Associates, Inc. (GAI),⁴⁶ an independent public relations specialist affiliated with FDAH since 1998. FDAH contacted GAI in an effort to begin a "communications outreach plan to respond to the recall."⁴⁷ This outreach effort included contact with "veterinarians, veterinary medical associations and key contacts in the animal health community and members of Congress and others believed to have influence at FDA and to continue to monitor and provide online coverage of the recall."⁴⁸

Ms. Germinder informed Committee staff that she recalled receiving instructions from Craig Wallace "sometime between September 6, 2004 and October 12, 2004,"⁴⁹ to google Victoria Hampshire.⁵⁰ GAI began forwarding internet research on Dr. Hampshire to Mr. Wallace on September 16, 2004.⁵¹ In response to the information on Dr. Hampshire, the Vice President of

meeting held on January 31, 2005, to examine the voluntary recall of ProHeart 6. See FDA Veterinary Medicine Advisory Committee (VMAC) Meeting, January 31, 2005, Committee Deliberations on Question 1 (Att. 4). Further, Dr. Riddell voted "YES" to the question "is ProHeart 6 safe for use in dogs?" *Id.* Whether or not the contacts that Dr. Riddell had with FDAH were disclosed to the FDA prior to his voting on the January 31, 2005, VMAC meeting is unknown. However, it appears that the contact he had with FDAH representatives was a component in FDAH's investigation of Dr. Hampshire.

⁴⁴ FTDO 001849 (Att. 14).

⁴⁵ Dr. Glickman was introduced by FDAH at the September 1, 2004, meeting as a consultant for FDAH. In addition, Dr. Glickman presented FDAH's study data at the January 31, 2005, VMAC meeting. See, VMAC January 31, 2005 Meeting Transcript (Att. 4). Dr. Glickman had gathered data used by FDAH to support the position that Pro Heart 6 was safe. It is unknown whether Wyeth informed FDA that FDAH had these contacts with Dr. Glickman.

⁴⁶ According to disclosures made by Ms. Germinder, FDAH has "utilized the services of Germinder & Associates, Inc. in a wide variety of projects since approximately 1998." Further, GAI has also contracted some projects with Wyeth Animal Health since 2004. However, GAI has "never had a general written contract with either of Wyeth's animal health divisions governing their relationship" and serves as "an independent contractor and executes projects with Fort Dodge Animal Health according to signed estimates which set forth a scope of work as directed by the Vice President of Marketing, Craig Wallace." See Letter from Pamela B. Stuart, Attorney for Lea Ann Germinder, to Senator Charles E. Grassley, May 16, 2006, at 5 (Att.15).

⁴⁷ *Id.* at 11.

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ FTDO 000879-881, 879 (Att. 16).

Pharmaceutical Research (Rami Cobb) for FDAH concluded that the information “helps to point towards there being a personal agenda on her part.”⁵²

Based on the information made available to my staff, FDAH hired more than one person to look into Dr. Hampshire’s activities. In fact, the Senior Vice President of North American Marketing at FDAH wrote to the Vice President of North American Marketing regarding the GAI research and said, “I had already hired an investigator to do the same.”⁵³ Ms. Germinder then sought further help and entered into a written contract with her nephew, Dan O’Hare, for independent consulting.⁵⁴

4. Failed Attempts to Purchase Competitors’ Prescription Products from AVA

The key portion of the investigation into Dr. Hampshire occurred in early October 2004 and revolved around Dr. Hampshire’s affiliation with a website she operated known as Advanced Veterinary Applications (AVA), <http://www.advancedvet.com>. As stated earlier, this was the website portal that Dr. Hampshire had created in 2000, prior to joining FDA. GAI and FDAH researchers came across AVA after Mr. Wallace asked for a google search of Dr. Hampshire.⁵⁵

Ms. Germinder stated that, once directed to the AVA website, she saw that it offered Heartguard, a competitor drug to ProHeart 6.⁵⁶ According to Ms. Germinder, once he became aware of this, Mr. Wallace instructed her to research this matter further and directed Ms. Germinder to attempt to make a purchase from the AVA website. In response, Ms. Germinder assigned one of her direct staff members, Catherine Couch, to “mystery shop” the AVA website.⁵⁷ Ms. Couch determined that the website was live and operational. Ms. Germinder noted that she then instructed her nephew Dan O’Hare, an independent consultant hired by GAI, to conduct internet research and attempt to make a purchase.⁵⁸

Mr. O’Hare made his first purchase of products from the AVA website on October 8, 2004. Mr. O’Hare placed an initial order for a product, Bitter Apple Spray—a non-prescription product—and paid \$6.08 for the product plus shipping cost. He used the business name XC Direct, billed the purchase to his father’s credit card and shipped it to his father’s home.⁵⁹ This order was shipped to Mr. O’Hare from VetCentric on October 11, 2004.⁶⁰

⁵² FTDO 000882-887 (Att. 17).

⁵³ FTDO 000888-893 (Att. 18).

⁵⁴ GA-9-00001-03 (Att. 19).

⁵⁵ See Letter from Pamela B. Stuart, Attorney for Lea Ann Germinder, at 11 (Att. 15).

⁵⁶ *Id.*

⁵⁷ Letter from Pamela B. Stuart, Attorney for Lea Ann Germinder, at 11 (Att. 15).

⁵⁸ *Id.* at 11.

⁵⁹ Letter from Pamela B. Stuart, Attorney for Lea Ann Germinder, at 12 (Att. 15).

⁶⁰ FTDO 000045-000049 (Att. 21).

Ms. Germinder's employees then attempted to purchase prescription products from AVA website that were direct competitors to ProHeart 6. Ms. Germinder asked Mr. O'Hare to purchase Heartguard, a competitor product to ProHeart 6. Mr. O'Hare was unable to purchase the product through the AVA website.⁶¹ After being denied the product because he did not have a prescription for Heartguard and was not a friend, family member or former client that Dr. Hampshire worked with on the AVA website, O'Hare instead purchased \$1,197.65 worth of non-prescription pet products through the product link on the AVA website, including shampoos and pet treats.⁶²

Later, GAI enlisted the help of Dr. Steven A. Levy, a veterinarian at Durham Veterinary Hospital in Durham, Connecticut.⁶³ Since 1990, Dr. Levy has been a canine-lyme disease consultant for FDAH.⁶⁴ Dr. Levy, according to the information presented to the Committee, worked with Ms. Germinder in the past and agreed to attempt to purchase Heartguard from the AVA website. However, Dr. Levy was unsuccessful in purchasing Heartguard from AVA.⁶⁵ Documents produced to my staff show that Dr. Levy then requested assistance from a person named "Kelly." Kelly was to obtain Heartguard using a prescription issued by Dr. Levy on October 18 and October 19, 2004.⁶⁶ According to GAI's documents, Kelly had a prescription from Dr. Levy and also requested a prescription through AVA.⁶⁷ Kelly had problems accessing the VetCentric ordering site, so she called VetCentric.⁶⁸ She told VetCentric that she "had a prescription from [Dr. Levy] and a request for a prescription through Advanced Vet [AVA]" but that she wanted a prescription from AVA.⁶⁹ She told VetCentric that AVA was her.⁷⁰ This statement was false; according to Dr. Hampshire, neither "Kelly" nor Dr. Levy were clients of AVA. Ultimately, VetCentric did not fill any prescription through AVA.⁷¹ VetCentric personnel told Kelly that she could, however, purchase the Heartguard product using Dr. Levy's prescription.⁷² Therefore, both of Dr. Levy's attempts to purchase Heartguard through AVA without an AVA prescription were unsuccessful.

In addition to the attempts by Mr. O'Hare and Dr. Levy, Ms. Germinder initiated an attempt to purchase Heartguard from AVA by enlisting the help of a pet owner in Maine. That individual was also unsuccessful.⁷³ Ultimately, GAI failed in its attempts to purchase products competitive with ProHeart 6 from Dr. Hampshire's AVA website.

⁶¹ Letter from Pamela B. Stuart, Attorney for Lea Ann Germinder, at 12 (Att. 15).

⁶² FTDO 000799-0000801 (Att. 22). According to Dr. Hampshire, the friends, family and former clients who used the AVA website to obtain prescription medication seldom, if ever, purchased non-prescription products.

⁶³ FTDO 000050-000053 (Att. 23).

⁶⁴ Resume of Dr. Steven Levy, found at <http://www.durhamveterinary.com/cv.html> (Att. 20).

⁶⁵ Letter from Pamela B. Stuart, Attorney for Lea Ann Germinder, at 12. (Att. 15).

⁶⁶ FTDO 000054-55 (Att. 24).

⁶⁷ *Id.*

⁶⁸ *Id.*

⁶⁹ *Id.*

⁷⁰ *Id.* The letter from Kelly to Dr. Levy states that "I'm not sure about identifying Advanced Vet as my vet, but this seemed the only way to proceed with the order."

⁷¹ *Id.*

⁷² *Id.*

⁷³ Letter from Pamela B. Stuart, Attorney for Lea Ann Germinder, at 12 (Att. 15)..

5. Interim Report Provided to Wyeth by Germinder & Associates

GAI produced its first report to Wyeth regarding Dr. Hampshire on October, 12, 2004.⁷⁴ This interim report consisted of information and research conducted, “in accordance with standard public relations research practices for background use only to determine the stakeholders who are conducting a negative communications campaign against ProHeart 6.”⁷⁵ The report was designed with the “hope that understanding who these stakeholders are, what motivates them, the tactics they use, and the key messages they wish to convey will assist you in executing your business strategy regarding this matter.”⁷⁶

The interim report produced by GAI contains (1) screen prints of internet searches of the terms “Victoria Hampshire” and “Tori Hampshire;”⁷⁷ (2) various scholarly articles authored and/or peer reviewed by Dr. Hampshire;⁷⁸ (3) screen prints of the AVA website operated by Dr. Hampshire and information about VetCentric;⁷⁹ and (4) information on the “Dogs Adverse Reactions” website and other websites that appeared critical of ProHeart 6.⁸⁰

6. Hiring a Private Investigator to Research Dr. Hampshire

In the days following the transmittal of the GAI interim report to FDAH, Ms. Germinder was in contact with Mr. Wallace on a daily basis.⁸¹ However, she realized that she needed some experienced assistance in furthering the investigation. Consequently, Ms. Germinder contacted a longtime acquaintance, Ms. Donna Dauite, a licensed private investigator.⁸² Ms. Dauite was tasked with tracking down proper legal ownership of the AVA website and was contracted by GAI to conduct this work.⁸³ During interviews with Committee staff, Ms. Germinder recalled that the decision to hire and contract with Ms. Dauite was discussed with Mr. Wallace and representatives of Wyeth prior to signing the contract. Specifically, Ms. Germinder told Committee staff on March 12, 2007, that she advised Mr. Wallace that further research would be done by a researcher who had credentials as a private investigator.

Ultimately, the GAI investigators, including Ms. Dauite, created a substantial investigative file on Dr. Hampshire. This file included property records for Dr. Hampshire’s personal residence,⁸⁴ business search records related to AVA,⁸⁵ taxation

⁷⁴ GA-4-00009 (Att. 25); GA-4-00134-231 (Att. 26).

⁷⁵ GA-4-00009 (Att. 25).

⁷⁶ *Id.*

⁷⁷ *See* GA-4-00135-00138 (Att. 26).

⁷⁸ GA-4-00159-00184 (Att. 26).

⁷⁹ *Id.*

⁸⁰ *Id.*

⁸¹ Letter from Pamela B. Stuart, Attorney for Lea Ann Germinder, at 12 (Att. 15).

⁸² *Id.*

⁸³ *Id.*

⁸⁴ GA-4-00041 (Att. 27).

⁸⁵ GA-4-00043 (Att. 28); 00045 (Att. 29).

records related to both Dr. Hampshire and AVA,⁸⁶ as well as records related to the VetCentric Prescription fulfillment site.⁸⁷

This information and over \$1,000 in over-the-counter, non-prescription animal products that Mr. O'Hare purchased from the VetCentric component linked to the AVA website and provided to GAI were given to Wyeth in two separate packages. The first package was delivered by Ms. Germinder on October 20, 2004,⁸⁸ and included "the latest correspondence and documentation in attempting to order Heartguard from Advanced Veterinary Applications"⁸⁹ as well as two boxes of "product and paperwork." GAI delivered the remaining information to Wyeth on October 27, 2004.⁹⁰

7. Meeting between Wyeth and Former FDA Commissioner

Emails produced to my staff detail at least two phone calls between Wyeth and senior FDA officials following Wyeth's receipt of GAI's October 27 production.⁹¹ Specifically, internal Wyeth documents show that Geoffrey Levitt, Vice President & Chief Counsel, Regulatory and Research at Wyeth, spoke with then-FDA Chief Counsel Dan Troy on November 5, 2004, in an effort to follow up on a call made to then-FDA Commissioner Crawford by Wyeth Chairman, Robert Essner.⁹² Based upon documents provided by FDA, it appears that the topic of conversation for both calls was "the apparent conflict of interest issue."⁹³ Further, emails obtained from FDA show that Wyeth prepared company-wide talking points on the issue, and that Wyeth believed they had "information to show not only that there was a strong appearance of conflict and bias, but also that these issues had influenced the data and analysis on which FDA's position was based."⁹⁴ The emails also show that Wyeth requested a meeting to discuss the issues with then-FDA Commissioner Crawford.

Wyeth created a 29-page slide presentation titled, "ProHeart 6: Apparent Conflict of Interest" and a 10-page appendix slide presentation with supporting documentation.⁹⁵ Both slide presentations appear to have been created based upon information obtained from the GAI investigation and Wyeth's own investigation of Dr. Hampshire.⁹⁶ Wyeth offered the slide presentations to FDA at a meeting on November 19, 2004.⁹⁷ This

⁸⁶ GA-4-00044 (Att. 30); 00047-52 (Att. 31); 00055-57 (Att. 32).

⁸⁷ GA-4-00053 (Att. 33).

⁸⁸ GA-4-00031 (Att. 34).

⁸⁹ *Id.*

⁹⁰ GA-4-00058 (Att. 35).

⁹¹ See FTDO 002613 (Att. 36).

⁹² *Id.*

⁹³ *Id.*

⁹⁴ *Id.*

⁹⁵ See Wyeth's November 19, 2004 slide presentation (Att. 8).

⁹⁶ Similar web searches and document searches on Dr. Hampshire were conducted concurrently to the investigation conducted by GAI. One noteworthy portion of this Wyeth investigation is the involvement of FDAH Senior Vice President & Chief Counsel C.T. Newsum, as many documents related to Mr. Newsum were withheld from the Committee by Wyeth under Attorney Client Privilege related to Mr. Newsum's capacity as FDAH's Chief Counsel. The Committee is not subject to such common law privilege, but took no action to force production.

⁹⁷ See Letter from Douglas Dworkin, Wyeth Pharmaceuticals, to Senator Charles Grassley, December 16, 2005, at 3 (Att. 37).

meeting took place at the FDA. Representing Wyeth were “Bob Essner, Chairman, President, and Chief Executive Officer; Jeff [sic] Levitt, V.P. and Chief Counsel Regulatory and Research; Gerald Fisher, Senior V.P., Drug Safety and Metabolism.”⁹⁸ The FDA was represented by then-FDA Commissioner Crawford, then-Chief Counsel Dan Troy, and Policy Analyst Dana Delman.⁹⁹ The topic of conversation was “issues surrounding the September 3, 2004, withdrawal from the market of ProHeart 6” and included discussion of “a potential conflict of interest issue.”¹⁰⁰ This portion of the meeting included Wyeth’s slide presentation regarding Dr. Hampshire.¹⁰¹ The presentation alleged, among other things, that (1) public records revealed that AVA was an “active internet veterinary pharmacy” selling products competing with ProHeart 6, which raised the appearance of a conflict of interest; (2) Dr. Hampshire was biased because she had been in contact with anti-ProHeart6 activists; and (3) Dr. Hampshire presented adverse events data in a biased fashion.”¹⁰²

8. FDA Investigation of Dr. Hampshire

Following the meeting between representatives from Wyeth and FDAH, then-FDA Commissioner Crawford and then-Chief Counsel Troy provided Wyeth’s slide presentation to Dr. Steven Sundlof, then-Director of CVM. Dr. Sundlof relayed the contents of the presentation via telephone to a Special Agent within the FDA’s Office of Internal Affairs (OIA) Office of Criminal Investigations (OCI) on November 22, 2004. According to the FDA, OIA “is a subordinate office within OCI which conducts administrative and criminal investigations of alleged employee misconduct.”¹⁰³ Based on this referral phone call, Special Agents within OIA opened an initial investigation into Dr. Hampshire on November 24, 2004, alleging that Dr. Hampshire was operating an internet pharmacy.¹⁰⁴

In the meantime, Dr. Hampshire continued to work with CVM staff on ProHeart 6 and began preparing for a January VMAC meeting.¹⁰⁵ She was unaware of Wyeth’s allegations and the FDA/OIA investigation. However, Dr. Hampshire informed Committee staff that her colleagues began to give her “a cold shoulder treatment,” but she did not know why.¹⁰⁶

Throughout December 2004, Dr. Hampshire continued to help select candidates for the January 2005 VMAC meeting. However, Dr. Hampshire was kept away from preparing the CVM presentation that would be given to the VMAC, despite her long history of working on ProHeart 6. During this same time, Mr. C.T. Newsum, Senior Vice President and Chief Counsel for FDAH, was working closely with the OIA agents.

⁹⁸ FDA Memorandum of Meeting prepared by Dana Delman, Policy Analyst, November 19, 2004 (Att. 38).

⁹⁹ *See id.*

¹⁰⁰ *Id.*

¹⁰¹ *See* Letter from Douglas Dworkin, Wyeth Pharmaceuticals, at 3 (Att. 37).

¹⁰² Wyeth’s November 19, 2004 slide presentation (Att. 8).

¹⁰³ Letter from David Boyer, then-Assistant Commissioner for Legislation, FDA, to Senator Charles Grassley, June 7, 2006, at 1 (Att. 39).

¹⁰⁴ FDA Office of Internal Affairs, Case Initiation and Fact Sheet, November 24, 2004 (Att. 42E).

¹⁰⁵ Letter from Dr. Victoria Hampshire to Senate Finance Committee, April 11, 2005 (Att. 1).

¹⁰⁶ *Id.*

Documents and information show that Mr. Newsum reached out to FDA agents on December 9, 2004, and was interviewed by OIA agents on December 16, 2004.¹⁰⁷ According to one of the FDA agents interviewed by Committee staff, Mr. Newsum called frequently regarding this matter. In fact, one written investigative report stated that Mr. Newsum spoke to an agent on “numerous occasions over the course of this investigation.”¹⁰⁸ Eventually, OIA agents pulled Dr. Hampshire’s ethics filings from the Office of Ethics at FDA where they learned that she filed three separate outside activity reports (OAR), including one for AVA Consulting.¹⁰⁹

The FDA/OIA investigation into Dr. Hampshire included (1) pulling Dr. Hampshire’s ethics forms; (2) reviewing the materials prepared by Wyeth; (3) interviewing the Chief Counsel for FDAH; (4) pulling all emails and internet activity from Dr. Hampshire at FDA; and (5) requesting the Department of Health and Human Services, Office of the Inspector General (HHS/OIG)¹¹⁰ to issue a subpoena to VetCentric for records related to AVA.¹¹¹ Based on this information, the OIA presented investigative facts relating to Dr. Hampshire’s alleged conflicts to officials at CVM on January 6, 2005.¹¹²

On January 7, 2005, Dr. Hampshire was called into a meeting with then-CVM Deputy Director Tollefson and OSC Director McChesney.¹¹³ Dr. Hampshire informed my staff that, during this meeting, Dr. Tollefson told her that Wyeth had “pulled all plugs” at the level of the Commissioner and that Dr. Hampshire was being reassigned.¹¹⁴ Dr. Hampshire agreed that if the industry sponsor had questions about her involvement that it was ultimately better to leave the role of lead reviewer for ProHeart 6 and let the data speak for itself. Accordingly, Dr. Hampshire then asked if she could be reassigned within CVM instead of being transferred out of the Center.¹¹⁵ Dr. Hampshire was granted a move within CVM, but was no longer a lead reviewer on ProHeart 6. She

¹⁰⁷ Letter from David Boyer, then-Assistant Commissioner for Legislation, FDA, to Senator Charles Grassley, June 7, 2006, Documents at Tab C (Att. 40).

¹⁰⁸ OIA Investigative Report January 31, 2005, at 3 (Att. 42B).

¹⁰⁹ *Id.*

¹¹⁰ It is important to note that during the time-frame discussed in this Letter, FDA held a distinction within the Department of Health and Human Services (HHS) not afforded to other subordinate agencies. The FDA had a written memorandum of understanding (MOU) with HHS/OIG regarding the investigation of internal misconduct by FDA employees. Att. 41. This MOU was executed in July 1998 and allowed FDA to continue to have Criminal Investigators, Federal Series 1811 employees, on staff in the Office of Internal Affairs to conduct investigations into employee misconduct. *Id.* Further, the MOU provided that both FDA/OIA and HHS/OIG would hold concurrent responsibility for investigating employee misconduct at FDA with FDA/OIA taking a lead role unless it was preempted by the HHS/OIG’s right in all cases to pursue a case jointly with OIA or after consultation replace OIA as the primary Agency. *Id.* Because of this right of preemption retained by HHS/OIG, FDA/OIA utilized the services of HHS/OIG whenever it needed to issue a subpoena duces tecum, as was the case here. The MOU was, however, withdrawn as of November 30, 2007, and the function of criminal investigation of FDA employees was returned to HHS/OIG “[t]o ensure integrity in the process of conducting sensitive employee misconduct investigations.” Att. 53. According to HHS/OIG, “this function is more appropriately placed in an investigative office with statutory independence.” *Id.*

¹¹¹ OIA Investigative Report, January 31, 2005, at 4 (Att. 42B).

¹¹² *Id.*

¹¹³ Letter from Dr. Victoria Hampshire to Senate Finance Committee, April 11, 2005 (Att. 1).

¹¹⁴ *Id.*

¹¹⁵ *Id.*

continued, however, to provide advice to CVM to keep continuity in CVM as they moved toward the advisory committee hearing.

During the next few weeks, CVM prepared for the January 31, 2005, VMAC to discuss the safety of ProHeart 6. One of Dr. Hampshire's colleagues was selected to make the presentation in place of Dr. Hampshire. On January 30, 2005, the Director of OSC called Dr. Hampshire at home and asked her to help prepare a statement for the VMAC in the event that questions arose about why Dr. Hampshire was not presenting.¹¹⁶ In response to this request, she helped prepare a statement that said she was on vacation and had been reassigned within FDA to different projects.¹¹⁷

On January 31, 2005, the VMAC met to discuss the safety of ProHeart 6 and the earlier recall. The panel heard data from both FDA and Wyeth. The presentation by FDA included testimony from CVM employees who relayed the same concerns that were presented by Dr. Hampshire at the September 1, 2004, meeting with Wyeth. The panel, by an 8-7 vote, ultimately concluded that safety concerns based on serious adverse events warranted the continued recall of ProHeart 6.¹¹⁸

With the VMAC complete, and following her reassignment to another division within CVM, Dr. Hampshire was still unaware of the investigation into her activities. However, on February 8, 2005, she was contacted by the FDA Office of Ethics regarding her outside activities reports.¹¹⁹ The Ethics staff asked Dr. Hampshire why she did not include her AVA website on her December 14, 2004, HHS Form 520-1 "Request for Approval of Outside Activity," or OAR.¹²⁰

Dr. Hampshire told my staff that she informed the ethics staff that the AVA website account was not included on her OAR because, even though it was still open, she had not been using it over the past year. She believed that she did not have to disclose an activity that was not producing income.¹²¹ This belief was wrong, and the Director of Ethics informed Dr. Hampshire that "receipt of income" was not the standard for filing an approved outside activity request. Dr. Hampshire was also told that because she had not ended the AVA activity, she also needed to file a new OAR in order to close the 2004 file.¹²² Dr. Hampshire agreed to file a new OAR report.¹²³ Dr. Hampshire did not know

¹¹⁶ *Id.*

¹¹⁷ *Id.*

¹¹⁸ VMAC meeting minutes, January 31, 2005 (Att. 50).

¹¹⁹ Letter from David Boyer, then-Assistant Commissioner for Legislation, FDA, to Senator Charles Grassley, June 7, 2006, Documents at Tab A – Email from Office of Ethics to Dr. Hampshire Feb. 8, 2005 (Att. 42).

¹²⁰ *Id.* at p. 14 (Att. 42).

¹²¹ *Id.* Because Dr. Hampshire seldom checked the website, she had no idea that GAI had ordered thousands of dollars of non-prescription supplies from the website, which gave it the appearance of being active. See Letter from Dr. Victoria Hampshire to the Senate Finance Committee dated April 11, 2005 (Att. 1).

¹²² Letter from David Boyer, then-Assistant Commissioner for Legislation, FDA, to Senator Charles Grassley, June 7, 2006, Documents at Tab A – Email from Office of Ethics to Dr. Hampshire Feb. 8, 2005 (Att. 42, Exh. 6).

¹²³ *Id.*

that the request from the Office of Ethics was not initiated by that office, but was requested as part of the investigation being conducted by OIA.¹²⁴

a. Re-Submission of Dr. Hampshire's Ethics Filings

Dr. Hampshire submitted her updated OAR on February 8, 2005 pursuant to the Office of Ethics request.¹²⁵ She continued to correspond with the Director of Ethics and other officials within the Office of Ethics and CVM regarding her disclosures.¹²⁶ On the morning of February 11, 2005, Dr. Hampshire was still unaware of the ongoing investigation into her activities. Later that day, Dr. Hampshire had lunch with a friend who was also employed at the CVM, who informed her that there was an investigation ongoing and that she should consider other employment.¹²⁷ This colleague informed Dr. Hampshire that representatives from Wyeth had obtained information about AVA and that they were looking into her outside activity.¹²⁸

Dr. Hampshire told Committee staff that, upon hearing this, she began to fear that she did not adequately detail the AVA website on her disclosure forms.¹²⁹ As a result of this, Dr. Hampshire said that she returned to her office and called Dr. Sundlof's assistant to ask if it was too late to attach a new comment sheet to her OAR.¹³⁰ She was informed that Dr. Sundlof had not reviewed the OAR yet.¹³¹ Dr. Hampshire then retrieved the disclosures she had prepared and given to Dr. Sundlof as a result of the February 8th conversations from the pile of OARs that were waiting to be signed by CVM Director Sundlof.¹³² Dr. Hampshire told Committee staff that she thought that, in responding to questions by Office of Ethics staff, she should add a new comments page indicating that AVA website contained an internet pharmacy component.¹³³ Dr. Hampshire placed a pink note on the documents noting the new detailed version of the OAR.¹³⁴ According to Dr. Hampshire, she was under the mistaken impression that her supervisors and officials in the Office of Ethics had not yet read the form and that submitting it as amended was insignificant.

On Monday, February 14, 2005, after receiving the copy of Dr. Hampshire's amended outside activities form, the OIA agent called the Office of Ethics that had reviewed Dr.

¹²⁴ Specifically, one of the Agents wrote in the OIA investigative report that he asked Ethics to request an update from Dr. Hampshire on her outside activities. OIA Investigative Report January 31, 2005, at p. 3 (Att. 42B). This request initiated the exchange on February 8, and all documents obtained and communications with Dr. Hampshire were transmitted by Ethics to OIA. Individuals within the Office of Ethics were prohibited from replying to Dr. Hampshire's inquiries until Ethics personnel consulted with OIA Agents investigating Dr. Hampshire. (Letter from David Boyer, Documents at Tab A—Email from Office of Ethics to Dr. Hampshire Feb. 8, 2005) (Att. 42).

¹²⁵ Dr. Hampshire's OAR form (Att. 42A).

¹²⁶ Letter from David Boyer, Documents at Tab A—Emails between Dr. Hampshire and various FDA personnel. (Att. 42).

¹²⁷ Letter from Dr. Victoria Hampshire to Senate Finance Committee, April 11, 2005 (Att. 1).

¹²⁸ *Id.* This friend was later disciplined for advising Dr. Hampshire of the on-going investigation.

¹²⁹ Dr. Hampshire's OIA statement (Att. 42A).

¹³⁰ *Id.*

¹³¹ *Id.*

¹³² *Id.*

¹³³ Letter from Dr. Victoria Hampshire to Senate Finance Committee, April 11, 2005 (Att. 1).

¹³⁴ *Id.*; Dr. Hampshire's OIA statement (Att. 42A)

Hampshire's OAR and asked "why four members in the chain of command would sign off on that document."¹³⁵ Dr. Wardrop, CVM's Chief Executive Officer, replied that he had not seen an OAR with such language and pulled a copy from his personal safe that did not include the additional language that Dr. Hampshire included in her amended form.¹³⁶ These originals without the additional language were sent to OIA on February 17, 2005, by the Office of Ethics.¹³⁷

b. Criminal Referral to the United States Attorney's Office for the District of Maryland

At this point the OIA Agents still had not spoken with Dr. Hampshire. Aside from the information her colleague provided to her at lunch, Dr. Hampshire said she had no knowledge of the ongoing criminal investigation, and that she changed the OAR because of her concern over her co-worker's warning.¹³⁸ She erroneously believed that amending the form was innocuous.¹³⁹

OIA agents prepared and submitted a referral letter to the United States Attorney for the District of Maryland (USAO).¹⁴⁰ This referral recommended prosecution of Dr. Hampshire for criminal violations of conflict of interest statutes, as well as for false statements to government officials.¹⁴¹ The language of the referral letter indicates that OIA was unaware of some of the facts, however. For instance, the referral letter stated, "Through the web portal of Advanced Veterinary Applications (AVA), the subject [Dr. Hampshire] also advertises heartworm medications which compete with Pro Heart 6. An agent acting on behalf of Fort Dodge Animal Health had two orders filled through AVA."¹⁴² This statement is inaccurate. FDAH had failed to get any orders for heartworm medication filled through AVA.

The referral letter also notes that, of the \$774.55 received from 2002 through 2005 for VetCentric orders, \$472.57 was paid to Dr. Hampshire from the orders placed by the agent for Fort Dodge Animal Health "to cement their Conflict of Interest Allegation. In this regard it is the opinion of the investigating agent that although the dollar amount may seem minimal, as an employee of the FDA, the subject has a grave and continuing conflict of interest."¹⁴³ This statement is also inaccurate.

¹³⁵ OIA Investigative Report, March 7, 2005, at 3 (Att. 42A).

¹³⁶ *Id.*

¹³⁷ *Id.*

¹³⁸ *Id.*

¹³⁹ *Id.* (Dr. Hampshire's OIA statement); Letter from Dr. Victoria Hampshire to Senate Finance Committee, April 11, 2005 (Att. 1).

¹⁴⁰ Referral Letter from FDA Office of Internal Affairs to Assistant United States Attorney Dunne dated Feb. 23, 2005 (Att. 2).

¹⁴¹ *Id.*

¹⁴² *Id.*

¹⁴³ *Id.* The items ordered from the website were ordinary items not requiring a prescription. Moreover, Dr. Hampshire informed Committee staff that she was never paid for the VetCentric order, because she apparently threw away the check for that order, thinking it was junk mail. See Dr. Hampshire's Letter to Senate Finance Committee (Att. 1).

OIA told the USAO that “When an order is placed through [Dr. Hampshire’s] web site it is actually filled by a firm named VetCentric which fills and ships the order,” and that there was “no evidence of a Nexus between Dr. Hampshire ... and VetCentric.”¹⁴⁴ The letter nonetheless indicates that Dr. Hampshire’s 2003, 2004, and 2005 Confidential Financial Disclosure Reports were deficient because she does not mention that AVA had an internet pharmacy component.¹⁴⁵ While the letter recommended consideration of potential violations, it also noted that the investigation found, “no evidence to suggest the subject committed any fraud when compiling Adverse Event Reports for ProHeart 6.”¹⁴⁶ By letter dated February 24, 2005, the USAO declined criminal prosecution of Dr. Hampshire.¹⁴⁷

c. The Administrative Case against Dr. Hampshire

OIA continued to build an administrative case against Dr. Hampshire. On February 24, the same day the United States Attorney declined prosecution, OIA Agents notified Dr. Hampshire that they needed to speak with her.¹⁴⁸ Dr. Hampshire advised the Committee that she met with two OIA agents that afternoon. According to Dr. Hampshire, the FDA agents informed her that there had been an ongoing inquiry into her conduct and that this was no longer a criminal matter. More importantly, Dr. Hampshire was advised that the investigation had originated from information generated by Wyeth, including attempts to see if she would dispense heartworm prescription products without a valid veterinary client relationship.¹⁴⁹ OIA also informed Dr. Hampshire that OIA had attempted to obtain prescription products from the AVA website, downloaded all of her emails and internet usage, and had determined that most of her clients were friends and neighbors.¹⁵⁰ Next, OIA agents pressed Dr. Hampshire regarding the changes she made to her outside activities form and stated that the changes raised integrity issues.¹⁵¹

The OIA agents questioned Dr. Hampshire on various topics during the February 24, 2005, interview, including details of her amendment to the OAR on February 11. One of the agents told Dr. Hampshire that he had been one of the people attempting to order heartworm medication to see if she would dispense the product without a prescription or a valid veterinary client relationship.¹⁵² Further, according to Dr. Hampshire, the OIA agents referred to contacts she made with Congressman Van Hollen, who had asked FDA about her reassignment, and asked her if she had “called off the congressman.”¹⁵³ Dr.

¹⁴⁴ Referral Letter from OIA to the United States Attorney’s Office dated Feb. 23, 2005 (Att. 2).

¹⁴⁵ *Id.* Ironically, Dr. Hampshire’s retrieval of her 2005 Confidential Financial Disclosure Report was for the purpose of clarifying that AVA had a link to an internet pharmacy—a clarification for which she was referred for criminal prosecution.

¹⁴⁶ *Id.*

¹⁴⁷ Letter from Asst. United States Attorney Dunne to FDA Office of Internal Affairs, February 24, 2005 (Att. 43).

¹⁴⁸ Letter from Dr. Victoria Hampshire to Senate Finance Committee, April 11, 2005 (Att. 1).

¹⁴⁹ *Id.*

¹⁵⁰ OIA Investigative Report, March 7, 2005, at 3 (Att. 42A).

¹⁵¹ *Id.*

¹⁵² Letter from Dr. Victoria Hampshire to Senate Finance Committee, April 11, 2005 (Att. 1).

¹⁵³ *Id.*; see also OIA Investigative Report, March 7, 2005 (Att. 42A); Dr. Hampshire informed my Committee staff that the OIA Agents specifically questioned her during their interview about the confidential communications between Dr. Hampshire and a member of Congress. While it appears this line

Hampshire provided OIA a sworn statement regarding the events surrounding her OAR amendment.¹⁵⁴ Finally, she informed OIA that other veterinarians at CVM utilized VetCentric prescribing accounts as part of their outside activities, in addition to other third party prescription filling houses.¹⁵⁵

d. Remark by a Wyeth Sales Representative about Dr. Hampshire

The investigation into Dr. Hampshire remained open into the summer of 2005. The next entry into her OIA case file indicates that, during the summer, FDA received a letter from a veterinarian who was outraged by disparaging remarks a Wyeth field representative made about Dr. Hampshire.¹⁵⁶ This veterinarian wrote that a Wyeth field representative told her that Dr. Hampshire, “had generated \$70,000.00 in one year from competitor product sales.”¹⁵⁷ Further, this veterinarian reported that the Wyeth representative said that Wyeth had Dr. Hampshire “investigated by private detectives.” This Wyeth representative went on to say that information about Dr. Hampshire’s financial interests “had all been verified.”¹⁵⁸ Finally, the Wyeth representative stated that once Dr. Hampshire was “taken care of,” the adverse event reports would drop off and that the product would return to the market.¹⁵⁹

Upon receiving this letter and determining that the letter contained “egregious claims,” OIA decided that the matter was “best handled with a formal response to Fort Dodge Animal Health [Wyeth] by FDA legal counsel.”¹⁶⁰ No formal correspondence from FDA Legal Counsel to Wyeth regarding this referral from OIA was ever produced to my staff. Mr. Secretary and Commissioner von Eschenbach, I reiterate my official request for a copy of that correspondence, if it exists.

Ultimately, OIA reported its findings of the investigation to then-CVM Director Sundlof via the CVM Executive Officer.¹⁶¹ The Executive Officer for CVM reported back to the OIA agents on July 19, 2005, that Dr. Hampshire and the colleague who tipped her to the ongoing OIA investigation were both provided “a verbal reprimand and counseling by their supervisors and a memo documenting these actions was completed and retained by their respective supervisors.”¹⁶² The OIA case against Dr. Hampshire

of questioning was only cursory, it must be noted that retaliation by federal agencies for contacting Congress is not new and could be construed as intimidation for protected whistleblowing in violation of the Whistleblower Protection Act, among other federal statutes.

¹⁵⁴ Although OIA alleged to the United States Attorney’s Office in its referral letter (Att. 2) that Dr. Hampshire received \$774.55 from Oct. 21, 2003 through February 23, 2005, Dr. Hampshire has informed Committee staff that she only received around \$200, because she accidentally threw away a check for \$472.57, thinking it was junk mail. Letter from Dr. Hampshire, April 11, 2005 (Att. 1). Technically, however, the website generated \$774.55 over that time period.

¹⁵⁵ OIA Investigative Report, March 7, 2005, at 4 (Att. 42A).

¹⁵⁶ Letter dated 2005 (redacted by Committee Staff) (Att. 55); OIA Investigative Report, September 2005, at 2 (Att. 42D).

¹⁵⁷ *Id.*

¹⁵⁸ *Id.*

¹⁵⁹ *Id.*

¹⁶⁰ OIA Investigative Report, Sept. 23, 2005, at 2 (Att. 42D).

¹⁶¹ OIA Investigative Report, June 8, 2005, at 2 (Att. 42C).

¹⁶² OIA Investigative Report, Sept. 23, 2005, at 2 (Att. 42D). Dr. Hampshire informed Committee staff that the OIA agent told her he was going to recommend that she be reprimanded for changing her OAR without

was closed by report dated September 23, 2005.¹⁶³ Despite the completion of the investigation and the determination by OIA that Dr. Hampshire committed no fraud in the adverse event report collection for ProHeart 6,¹⁶⁴ Dr. Hampshire was not provided an opportunity to return to her previous position.

III. Conclusions and Recommendations

The series of events set forth in this Letter describe the removal of the lead adverse drug coordinator on ProHeart 6 issues from her position, ostensibly at the request of an industry sponsor, without sufficient proof of wrong-doing. Although a conflict-of-interest allegation deserves serious attention, this investigation, which includes information readily available to the FDA (particularly FDA agents) at the time of the events described, has shown that the allegations presented by Wyeth in its November 19, 2004, slide presentation were misleading.

For instance, Wyeth informed FDA that Dr. Hampshire was operating an internet pharmacy.¹⁶⁵ The AVA website, however, was a portal from which customers could order products from VetCentric, which was an independent pharmacy. A customer ordering products had to click on a "store" button that would take the customer to the VetCentric link.¹⁶⁶ Wyeth was fully aware that orders for products were sent to VetCentric for processing, shipping, and invoicing, because it so informed FDA during its November 19, 2005, slide presentation.¹⁶⁷

Wyeth also told FDA that, because Dr. Hampshire's AVA website offered access to one or more products sold by VetCentric that were competitive with Wyeth's ProHeart 6, this demonstrated a conflict of interest. VetCentric, however, also offered ProHeart 6 (tablet form) and other Wyeth products.¹⁶⁸ Moreover, Dr. Hampshire informed the OIA agents that it is not uncommon at CVM for veterinarians to have similar arrangements with third-party fulfillment houses such as VetCentric.¹⁶⁹ The only significant activity on Dr. Hampshire's AVA site was, coincidentally, created by Wyeth itself. This may have resulted in the OIA agents' mistaking this activity as evidence of a "conflict of interest."¹⁷⁰ It appears that FDA agents failed to conduct a thorough investigation into the Dr. Hampshire matter prior to making a referral to the USAO.

In addition, Wyeth indicated to the FDA that Dr. Hampshire had inappropriate contacts with anti-ProHeart 6 activists.¹⁷¹ Although several activists did contact Dr.

getting permission from Dr. McChesney. She said that she was supposed to receive a written reprimand from Dr. McChesney, but that she did not receive one, nor has she seen one in her personnel file.

¹⁶³ *Id.* The report synopsized the issues, but did not set forth any findings.

¹⁶⁴ Referral letter from FDA-OIA to USAO dated Feb. 23, 2005 (Att. 2).

¹⁶⁵ See Wyeth's November 19, 2005 slide presentation (Att. 8).

¹⁶⁶ GAI's Interim Research Report, Oct. 12, 2004, Bates GA-4-00202 (Att. 26).

¹⁶⁷ Wyeth's November 19, 2005 slide presentation at p. 8.

¹⁶⁸ Dr. Hampshire's Rebuttal to Wyeth's slide presentation (Att. 44).

¹⁶⁹ OIA Investigative Report, March 7, 2005, at 4 (Att. 42A).

¹⁷⁰ See Letter of Referral from FDA Office of Internal Affairs to Assistant United States Attorney Dunne (Att. 2).

¹⁷¹ See Wyeth Nov. 19, 2004 slide presentation (Att. 8).

Hampshire, such contacts were to report adverse events and her responses to these contacts were well within her job description.¹⁷² Finally, the two emails offered by Wyeth to demonstrate that Dr. Hampshire's peers feared that she was on a vendetta came from two veterinarians with ties to FDAH (see footnotes 43, 45). That information, however, was not revealed by Wyeth to the FDA.

The allegations regarding Dr. Hampshire's bias against ProHeart 6, as pointed out above, were eventually rejected by FDA. Significant resources, however, were devoted to investigating Dr. Hampshire.¹⁷³ These resources may have been saved had the former FDA Commissioner, former Chief Counsel, and/or Director of CVM approached Dr. Hampshire and inquired about the information presented by FDAH. Instead, resources were expended by (1) two FDA/OIA Special Agents, (2) HHS/OIG, and (3) the USAO, not to mention (4) other offices within FDA. Further, the only violation that Dr. Hampshire committed and that was proven by FDA—amending her OAR forms—apparently happened because she learned of an investigation into her outside activities and panicked. Thus, it appears that Dr. Hampshire was verbally reprimanded as a result of the investigation conducted by the OIA agents and not as a result of any proactive campaign against an industry sponsor. By mishandling an investigation and submitting material to law enforcement that was rife with error, FDA not only wasted resources, it created serious doubts about the integrity of its processes.

Based upon these findings, I offer the following recommendations to the FDA and would appreciate your comments.

A. Require Formal Disclosure and Full Documentation of All Meetings Held by FDA Staff with Regulated Sponsors

At present, FDA regulations allow and encourage the FDA to accept requests for private meetings with every person outside the Federal Government.¹⁷⁴ These requests can be made by industry sponsors, as was the case with former FDA Commissioner Crawford agreeing to meet with Wyeth and FDAH representatives. The regulations state "An official transcript, recording, or memorandum summarizing the substance of any meeting described in this section will be prepared by a representative of FDA when the Agency determines that such documentation will be useful."¹⁷⁵

Because the standard for documenting meetings is discretionary, it could potentially allow meetings with senior FDA employees to go unrecorded. In the case of the November 19, 2004, meeting that then-FDA Commissioner Crawford and then-Chief Counsel Troy had with FDAH and Wyeth representatives, FDA officials made a

¹⁷² Dr. Hampshire's Rebuttal to Wyeth's slide presentation (Att. 44).

¹⁷³ GAI, the firm that investigated Dr. Hampshire, estimated that its investigation cost about \$20,000. Letter from Pamela Stuart, Attorney for Lea Ann Germinder, to Sen. Grassley, May 16, 2006 (Att. 15). We have no estimates from FDA regarding its expenditure of investigative man-hours, duplication of resources required to get Dr. Hampshire's replacement for the VMA meeting up to speed, and time spent by supervisors and others on this matter.

¹⁷⁴ 21 C.F.R. § 10.65(c) (2006).

¹⁷⁵ 21 C.F.R. § 10.65 (e) (2006) (emphasis provided).

determination that documentation of the meeting was necessary.¹⁷⁶ The documentation of the meeting on November 19th is sparse and unhelpful, however.

Regarding Dr. Hampshire, the memorandum notes that, “Wyeth representatives conveyed their concerns with the FDA assessment of adverse reaction data, and a potential conflict of interest issue.”¹⁷⁷ This is the only statement about the conflict of interest issue. This one sentence does not begin to describe Wyeth’s production and delivery to the FDA of more than 25 slides of information challenging Dr. Hampshire’s credibility. Further, the memorandum does not mention that this information was to be referred to the CVM Director for appropriate action. The bare-bones memorandum, which does not fully describe the events that transpired or the follow-up action that was recommended, thus effectively failed to disclose the real substance of the meeting. This is the sort of double standard that highlights the problem with transparency at the FDA: the transparency is there; you just can’t see it.

My Committee staff received no further documentation from the FDA regarding any of the other contacts or meetings that then-FDA Commissioner Crawford or other FDA officials had with Wyeth/FDAH. However, OIA agents informed Committee staff about numerous contacts between them and FDAH’s Chief Counsel.¹⁷⁸ The flow of information between OIA agents and FDAH’s Chief Counsel is of great interest to me. It appears that all the industry sponsor’s Chief Counsel had to do was to pick up the phone in order to contact an OIA agent. In order for me to converse with OIA, I have had to resort to obtaining a subpoena.

In addition, notes provided by Wyeth regarding a conversation between Dr. Corcoran of FDAH and Dr. Sundlof of the FDA, provide evidence of FDA’s release of pre-decisional information to the company. Clearly, documentation of these meetings and discussions would provide much-needed insight into the interactions between the FDA and industry sponsors, and whether such interactions are appropriate. Accordingly, I recommend that new policies and procedures be put in place that require formal disclosure and full documentation of all meetings held by FDA staff with regulated sponsors.

FDA’s failure to document has been brought to the FDA’s attention on numerous occasions. I am now seeking your assurance, Mr. Secretary and Commissioner von Eschenbach, that this issue will be promptly resolved.

B. Improved Management of Internal Investigations

This case represents, among other things, a breakdown in FDA’s internal investigation processes. Regarding the initial inquiry into Dr. Hampshire, then-CVM Director Sundlof chose not to discuss Wyeth’s allegations with Dr. Hampshire and instead referred the matter to OIA Special Agents. This led to a poorly handled investigation involving significant resources and created an environment of fear that

¹⁷⁶ See, Memorandum of Meeting between Wyeth and FDA Officials, November 19, 2004 (Att. 38).

¹⁷⁷ *Id.*

¹⁷⁸ See, FTDO 001654 (Att. 11).

apparently encouraged Dr. Hampshire to engage in the activity for which she was ultimately reprimanded—altering her ethics form.

I am not suggesting that all internal investigations of FDA employees be brought to the employees' attention. This case required a more thorough analysis of the facts and issues by the FDA to determine if the circumstances presented were merely a misunderstanding, or something else that required further action by law enforcement. In this instance, which may have been a unique situation, one question to Dr. Hampshire could have quickly resolved the matter. Asking Dr. Hampshire about her AVA website would, in all likelihood, not have compromised the investigation, nor would it have been anything other than a question that should—and could—be asked in a normal business setting.¹⁷⁹ Moreover, FDA should have independently examined the information Wyeth presented at the November 19, 2004 meeting.¹⁸⁰

Yet another example of questionable management involves the letter sent to the FDA from a veterinarian who was outraged by a Wyeth field representative's disparaging remarks regarding Dr. Hampshire.¹⁸¹ OIA apparently forwarded the letter to FDA Legal Counsel for appropriate action.¹⁸² No evidence of any follow-up by FDA, however, was provided to my staff. If there was any follow-up by FDA, I request that I be informed immediately.

Regarding the February 23, 2005, referral letter sent by OIA to the United States Attorney's Office for the District of Maryland, I request that both the HHS and FDA describe in detail any policies and procedures that will be put into place to ensure that future referrals to the USAO will not be riddled with inaccuracies. I would also like to know (1) whether the referral to the USAO was reviewed by FDA/HHS counsel and, if so, who reviewed it; (2) whether the referral was reviewed by any individual(s) other than

¹⁷⁹ Apparently, the practice of CVM veterinarians of using independent pharmacies, which Dr. Hampshire informed us was widely used at CVM, was not understood by FDA management or the OIA. After Dr. Hampshire explained the practice to management, CVM Ethics instated a clarification regarding the "Private Practice of Veterinarians," effective July 20, 2005, which states that "writing valid prescriptions to be filled by an independent pharmacy is entirely within the scope of veterinary practice" and "clearly acceptable as an outside activity for CVM employed veterinarians." See, "Outside Activity Process-Private Practice of Veterinarians." (Att. 54).

¹⁸⁰ One additional example of mismanagement occurred after the Committee's investigation was made public. On November 18, 2005, FDA spokesperson Susan Bro, who has since left the FDA, notified *Reuters* news service that the investigation into Dr. Hampshire was done with "Dr. Hampshire's knowledge." Letter from Senator Charles Grassley to Dr. Andrew von Eschenbach, Acting Commissioner, FDA, Nov. 30, 2005 (Att. 46). Further, Ms. Bro stated that the FDA investigation of Dr. Hampshire was not criminal, in direct contravention of the facts (*i.e.*, that a criminal referral had been made by OIA agents earlier that year in February 2005). Whether or not this was an intentional misstatement is unknown. However, it is difficult to understand why Ms. Bro made these statements, in light of the fact that Dr. Hampshire's attorney pointed out these inaccuracies to Ms. Bro's staff prior to the release of the statement. *Id.* This inaccurate statement to *Reuters* represents an instance where effective internal communication could have resulted in a correct response to the media. Further, despite un-contradicted evidence of this inaccuracy made to the press, FDA failed to set the record straight and correct the inaccurate statements made by Ms. Bro.

¹⁸¹ Letter dated summer, 2005 (redacted) (Att. 55).

¹⁸² OIA Investigative Report, Sept. 2005 (Att. 42D).

the signatory and, if so, who were the individual(s); and (3) who will be held accountable for this misleading letter.

C. New Procedures for Suspension of Advisory Panels when Sponsor Raises Allegations against FDA Employees

The FDA has guidance regarding conflicts of interest and advisory panel members, and conflict-of-interest reporting by FDA employees.¹⁸³ The case involving Dr. Hampshire raises questions, however, about yet another type of conflict of interest: a potential for targeted removal of FDA employees or panel participants who may not fully support the sponsor's views.

As part of this investigation, my Committee staff requested a list of all known OIA investigations since 1996 that were based on the complaints of industry sponsors.¹⁸⁴ There were several identifiable instances of such investigations. Although various reasons motivated these investigations, one common thread exists among all of the industry-initiated complaints to the FDA: there are no procedures at FDA to postpone advisory committee meetings when industry sponsors raise serious allegations against a panel participant and/or an FDA presenter. This potential loophole could allow industry sponsors to attempt to affect the votes of an advisory committee by removing individuals who possess information contrary to the sponsor's position. Therefore, I recommend that HHS and FDA create a list of requirements for those situations where industry sponsors seek to exclude an FDA employee from participating in an advisory committee meeting. The FDA should have the ability to potentially delay the proceeding until the allegations are substantiated or some other reasonable action is taken (a person with similar skills, qualifications, and understanding of the topic of the advisory committee meeting is up to speed with the presentation.) Although allegations of misconduct should always be taken seriously, they should not be acted upon without first conducting due diligence.

I look forward to hearing from both of you on how HHS and FDA intend to deal with these issues.

IV. Closing

Throughout my investigation, internal FDA sources revealed concerns and disagreements held by and between CVM scientists who are involved in the ongoing scientific review of ProHeart 6. In particular, my Committee staff has received

¹⁸³ The FDA has new draft guidance procedures for removing and recusing members from FDA advisory committees, such as the VMAC, when there are conflicts of interest posed by participation of certain members. See <http://www.fda.gov/oc/guidance/advisorycommittee.html>. The FDA code of conduct requires that employees disclose potential conflicts of interest, such as the form 450 OAR that Dr. Hampshire filed in this case. The code of conduct also requires these individuals to recuse themselves from any advisory committee should they have a real or apparent conflict of interest. Further, any FDA employees who are Commissioned Officers in the Public Health Service are bound by a similar code of conduct and ethics as part of their oath to the PHS. Therefore, supervisors should be aware of the need to recuse and police FDA employees accordingly.

¹⁸⁴ See Letter from David Boyer, then-Assistant Commissioner for Legislation, FDA, to Senator Charles Grassley, June 7, 2006, Documents at Tab E (Att. 45).

information which suggests that internal disagreement exists over whether or not old and new studies substantively address all historically reported major adverse events associated with ProHeart 6 use in dogs. By this Letter I am advising both of you that I am concerned that the scientific process is being compromised internally. In light of the findings presented in this Letter and the fact that FDA sources to this day continue to bring concerns about ProHeart 6 to my attention, I believe that involvement by FDA management at the highest levels may be necessary to ensure the integrity of FDA's processes. However, if it is decided that this matter does not need to be elevated to the highest levels, please advise me of that decision immediately.

While the details of this Letter are aimed at reforms at the FDA and the missteps made in investigating Dr. Hampshire both criminally and administratively, culpability does not lie with the FDA alone. It is uncontroverted that industry representatives ought to have a good working relationship with the FDA, but under no conditions should the scientific process be compromised by industry pressure.¹⁸⁵

Moreover, I would appreciate a personal assurance from both of you that no retaliation will be taken against any person who contributed, either directly or indirectly, regarding this Letter, or who may contribute to any future investigation of ProHeart 6 that I might undertake.

In closing, please provide a response to the concerns, findings and recommendations contained in this Letter by no later than February 25, 2008. Should you have any questions please feel free to contact Angela Choy or Elizabeth Rinaldo of my staff at (202) 224-4515. All formal correspondence should be sent via electronic transmission in PDF format or via facsimile to (202) 228-2131 and original by U.S. mail.

Sincerely,



Charles E. Grassley
Ranking Member

Attachments

¹⁸⁵ Additionally, the actions of Lea Ann Germinder were also problematic. Ms. Germinder's recollection of the events appears to be supported by the extensive documentation provided by GAI, including a contract with a private investigator. It appears that once the Committee inquiry into Wyeth's involvement in investigating Dr. Hampshire began, however, Ms. Germinder attempted to reduce her involvement, telling Committee Investigators that she did not understand why Wyeth had her do this investigation and that in hindsight it made her uneasy. These post-hoc sentiments aside, Ms. Germinder acted as the intermediary and coordinator for the private inquiry into Dr. Hampshire that led to the internal FDA investigation. While it was only one piece in the equation, her assistance to Wyeth, including hiring the private investigator, cannot be denied. Nonetheless, we appreciate Ms. Germinder's help and cooperation with our investigation.

Study 3014 Problem Sites

Name/Site	Audited by Aventis	Outcome	Significant GCP Violations
Dr. Barber/ 2340	No	Terminated from study	Refusal to communicate and comply with PPD or Aventis
Dr. Blanchard/ 1228	Yes		Protocol problems; no pregnancy testing documentation; PI entering date on informed consent
Dr. Franklin/ 24	No		No source records or medical charts; some patients undraged; low AE
Dr. Garner/ 881	Yes	Site closed to additional recruitment	PI self-enrolled; no source documentation; missing consent forms
Dr. Kaur Achreja/ 759	No	483 issued; disqualified	Data inconsistencies; backdating; didn't follow investigational plan; informed consent problems
Dr. Kirkman-Cambell/ 1129	Yes	Convicted	Signature and data irregularities; missing lab reports; lack of pregnancy testing; study coordinator was patient
Dr. Lang/ 96	Yes	483 issued	Lack of pregnancy testing; patients enrolled with penicillin allergies; informed consent problems
Dr. McLeod/ 2557	No	Received NIDPOE letter	No signatures on informed consent
Dr. Monticciolo/ 1654	No	483 issued; certificate	Nearly identical lab values
Dr. Salerno/ 1057	No	revoked	Cocaine use Failure to produce completed study forms and other standard documentation
Dr. Sarkar/ 1124	No	Terminated from study	Missing consent forms; unreported AEs; numerous documentation discrepancies; no drug
Dr. Sghatti/ 469	No		No dates on informed consent; no pregnancy testing documentation; other protocol problems
Dr. Shoemaker/ 211	Yes		No source documents; informed consent problems; no pre-therapy baseline labs
Dr. Stone/ 2259	Yes		Missing dates and signatures; informed consent problems
Dr. Tengco/ 606	Yes		Altered informed consent; protocol violations; patients missing required
Dr. Terpstra/ 1622	No		informed consent date problems; protocol adherence issues
Dr. Weiss/ 1630	Yes		

Dr Kirkman-Campbell Site What Aventis Knew:

- 1. Errors on nearly every informed consent form – date modifications; initials different from signature; study coordinator entering date for subjects and PI.**
- 2. Blatantly forged signature on informed consent form.**
- 3. Very limited medical records.**
- 4. Use of different colored ink on medical charts – overwrites/crossouts – inserts of diagnosis in different colored ink.**
- 5. Routine failure to give pregnancy test to women of childbearing age.**
- 6. Study Investigator and Coordinator unaware of definitions of Serious Adverse Event or Adverse Event of Special Interest.**

Dr Kirkman-Campbell Site What Aventis Knew:

- 7. No adverse events for the first 300 patients enrolled with drugs known to have adverse events.**
- 8. Lab results indicative of blood splitting (one patient's blood sample attributed to multiple patients).**
- 9. Lack of proper diagnosis for study eligibility.**
- 10. Subjects with no history of chronic bronchitis.**
- 11. Large numbers of patients randomized in the IVRS in a short increment of time when the office was closed for lunch and not seeing patients.**
- 12. 100% compliance by patients taking study medication.**